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OXFORD AMERICAN HANDBOOK OF NEUROLOGY

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Emphasis on common clinical presentations and differential diagnosis

Appendix of frequently used scales

Edited by
Sid Gilman, With Hadi Manji
Sean Connolly, Neil Dorward
Neil Kitchen, Amrish Mehta
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Oxford American Handbook of Neurology

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Oxford American Handbook of Neurology

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Preface

The Oxford Handbooks have been an extremely valuable adjunct to the education of physicians in multiple areas of medicine in the United Kingdom and in many other countries, principally those with linkages to the educational processes of medicine in the United Kingdom. These books have been less used in the United States, although they have been familiar to many in this country and greatly admired for their broad range of coverage, succinct presentations, easy accessibility, accuracy, and utility. *The Oxford Handbook of Neurology* has been one of these books, and it is widely used in the United Kingdom and other countries not only by medical students and trainees in neurology and neurosurgery, but also by internists, family physicians, and practitioners in many other fields of medicine. I have had the frequent experience of visiting hospitals in the United Kingdom and seeing house officers with an Oxford Handbook tucked into a pocket for easy, frequent access. When Oxford University Press first approached me to ask whether I might consider serving as editor of the *Oxford American Handbook of Neurology* in an edition developed specifically for the United States, I was immediately interested because of my familiarity with the utility and widespread use of the book elsewhere. Having accepted this position, I recruited a group of my colleagues here at the University of Michigan to put together a volume that would reflect modern neurology as practiced in the United States, with an approach that is up to date and modeled along the lines of the U.K. editions of the book.

This book adheres to the brevity and style of the U.K. edition. Nevertheless, this is a new book with entirely new presentations. As the topics are important in understanding how to approach neurological diagnosis, we have chosen to retain the first three sections of the U.K. edition, including the basics of the neurological history and examination; a succinct review of neuroanatomy; and common clinical presentations. After the third chapter, we have developed multiple individual chapters to capture the major categories of neurological disease. A good deal of the neurosurgery section in the U.K. edition has been redistributed to other chapters, and three individual chapters remain focused on neurosurgical topics. Owing to the emerging importance of this area in neurology, we have included a chapter devoted to sleep disorders. We have developed large numbers of new illustrations, both drawings and imaging studies. The imaging studies utilize the currently best-available techniques of magnetic resonance imaging (MRI) and computed tomography (CT) scanning.

In the past several decades, clinical neurology has evolved from a field focused principally upon diagnosis into a field in which multiple medical and surgical approaches can be symptomatically helpful and, for many diseases, can ameliorate or slow the progression of the underlying pathological process. Accurate diagnosis is essential and can be challenging. The process required includes obtaining a full chronological history of the patient's

complaint, including medications used, with appropriate past medical history, family history, system review, and social history, followed by a general medical and neurological examination. With this information at hand, the next step is to deduce the anatomical location(s) of the lesion or lesions that can evoke the clinical findings. This is followed by a determination of the disease processes that would be compatible with the history of disease evolution. At this point, laboratory investigations can further the inquiry, but bypassing the initial steps can lead to time-consuming, costly, unnecessary laboratory studies and frustrations on the part of both the clinician and the patient. Accordingly, this book contains information that will help the clinician to approach patients with neurological disorders, and the diseases described succinctly can serve as a guide to the disease processes that need to be considered in differential diagnosis.

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Acknowledgments

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Chapter 1

Neurological history and examination

Zachary London, MD

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Principles of neurological history taking

> The primary role of the examination becomes the testing of the hypotheses derived from the history.
>
> —William Landau

The usual approach to a clinical problem is to ask the following:

- Where is the lesion, e.g., brain, spinal cord, anterior horn cell, peripheral nerve, neuromuscular junction, muscle?
- What is the etiology, e.g., vascular, degenerative, toxic, infectious genetic, inflammatory, neoplastic, functional?
- What is the differential diagnosis?
- Is treatment possible?
- What is the prognosis?

A detailed history usually will yield more information than the neurological examination and ancillary tests.

- Family members and eyewitness accounts are essential, e.g., in patients with dementia or episodic loss of consciousness. Obtain a history by telephone if necessary.
- A review of outside records may be very useful.
- Analysis of symptoms will follow a similar plan:
  - Date/week/month/year of onset
  - Character and severity
  - Location and radiation
  - Time course
  - Associated symptoms
  - Aggravating and alleviating factors
  - Previous treatments
  - Remissions and relapses

Past medical history

Do not accept the patient's diagnostic terms, e.g., "migraine," "seizure," "stroke." Ask about specific symptoms.

Family history

Draw a family tree. Document specific illnesses and cause of death, if known. In particular, ask about the age and cause of death of the patient's parents. In certain communities, ask about consanguinity. If you are suspicious of an undiagnosed disease in a family member, ask about symptoms. For example, a family member with weakness and gait disturbance may have never been diagnosed with myopathy.

Social history

This should include inquiries regarding the following:

- Alcohol
- Smoking
- Occupation
- Recreational drug use
- Sexual history
- Detailed travel history
- Dietary habits

The general examination

- This starts on first meeting the patient; it is useful practice to bring patients back from the waiting room yourself. Gait disturbance, tremor, loss of facial expression, and dysarthria can often be identified while leading the patient from the waiting room to the examination room. General examination can provide valuable clues. Ideally all patients should be stripped to their underclothes.
- Cardiovascular system. Pulse, heart sounds, auscultation of the carotid arteries, blood pressure (lying down and standing after 3 minutes if any suggestion of autonomic involvement).
- Respiratory system. Diaphragmatic movement. May need to measure forced vital capacity (FVC) and negative inspiratory force (NIF) in patients with neuromuscular weakness.
- Gastrointestinal system. Palpate for hepatosplenomegaly or abdominal masses.
- Genitalia. In men, testicular examination should be considered. Rectal examination if malignancy is suspected or assessment of anal tone and sensation if cord or cauda equina compression in differential diagnosis.
- Breasts. Essential if neoplastic or paraneoplastic conditions are considered.
- Examine the spine. A hairy patch may indicate underlying spinal disorder or a dermal sinus. Auscultation over spine may reveal the bruit of a dural arteriovenous malformation (AVM).
- Skin. Melanoma, vasculitic rash, livedo reticularis, or vitiligo may suggest the presence of a systemic disease that may have neurologic manifestations.
- Head. Palpate the temporal arteries in elderly headache patients; auscultation may reveal a bruit. Palpate the trapezii for evidence of tenderness in muscle tension and cervicogenic headache.

Cranial nerve I (olfactory nerve)

- Patients may not recognize a problem unless it is essential for work or hobbies, e.g., chef. Furthermore, it may be difficult to tell whether patients have trouble with a specific smell because they have anosmia or because they are just not familiar with it.
- The nose is supplied by the olfactory and trigeminal nerves. Irritants like NH_3 stimulate the trigeminal nerve and may be misleading.
- Use the University of Pennsylvania Smell Identification Test (UPSIT) if available. Otherwise use bedside products, e.g., orange peel, coffee, chocolate, peppermint, or cinnamon. Ask if there is a smell (perception, peripheral process) and then identify it (cognitive, central process).
- Differential diagnosis for anosmia:
  - Viral infection
  - Head injury
  - Parkinson disease (PD)
  - Alzheimer disease (AD)
  - Refsum disease
  - Olfactory groove meningioma
  - Sjogren syndrome
  - Toxic (intranasal zinc, some antihypertensives, thyroid supplements)
  - Kallman syndrome (anosmia + hypogonadism, X-linked recessive)

Cranial nerve II (optic nerve and visual pathway)

Visual acuity

- Test distance acuity of each eye with an eye chart (see Fig. 1.1).
- Correction for refractive errors with glasses or using a pinhole.
- In papilledema, visual acuity is preserved unless chronic. In optic neuritis or infiltration, visual acuity is impaired.
- Color vision tested with Ishihara color plates.

Visual fields

- Assess visual fields by confrontation with each eye in turn using a red pin (5 mm red target), finger waving, or finger counting.

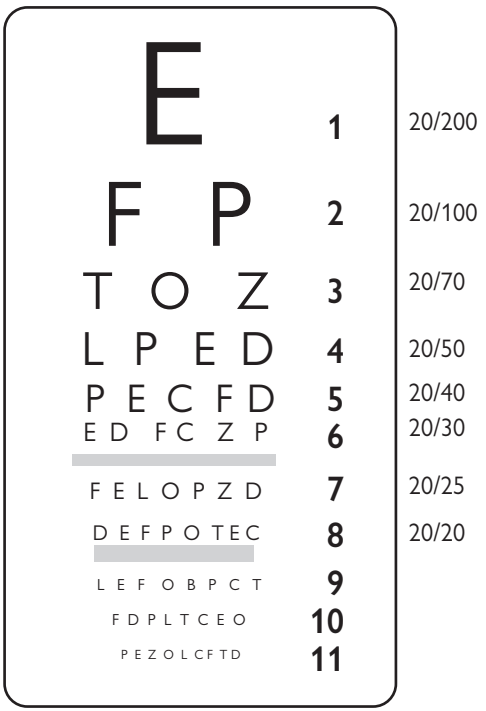

Figure 1.1 Snellen eye chart. Hold the chart about a foot in front of the face in good light. Test each eye separately, both with and without glasses.

- Goldmann perimeter is a bowl-shaped device and uses small light targets (kinetic).
- Humphrey is an automated technique (static).
- Visual inattention may indicate parietal lobe dysfunction.
- Uncooperative or aphasic patients—observe reaction to threat.

Visual field defects

- Monocular field defect: ocular, retinal, or optic nerve disorders.
- Constricted fields—glaucoma, chronic papilledema.
- Tunnel vision—retinitis pigmentosa or nonorganic.
- Central scotoma—optic nerve or macular disease.
- Altitudinal defects are due to retinal vascular lesions. Vessels do not cross the horizontal raphe.

Defects affecting both eyes may indicate a lesion of or behind the optic chiasm (vertical meridian). The common patterns of field loss are shown in Table 1.1. Figure 1.2 shows a diagram of visual field defects.

Clinical points

- Complete homonymous hemianopia indicates only that the lesion is behind the optic chiasm. The more posterior the lesion, the more congruous the defect.
- Macular sparing may occur in a posterior cerebral artery (PCA) stroke. The PCA supplies most of the visual cortex, but the occipital pole may be supplied by a branch of the middle cerebral artery (MCA).
- Junctional lesions between the optic nerve and chiasm affect ipsilateral optic nerve fibers and fibers from the inferior nasal retina of the opposite optic nerve as they loop after decussation.

Table 1.1 Common patterns of visual field loss

Field defect	Site of lesion(s)	Etiology
Homonymous hemianopia	Optic tract, optic radiation, occipital lobe	Stroke, tumor
Homonymous superior quadrantanopia	Temporal lobe	Stroke, tumor
Homonymous inferior quadrantanopia	Parietal lobe	Stroke, tumor
Bitemporal hemianopia	Optic chiasm	Pituitary adenoma, craniopharyngioma
Binasal hemianopia	Perichiasmal	Bilateral internal carotid artery aneurysms
Junctional scotoma	Junction of optic nerve and chiasm	Tumor
Bilateral scotomas	Occipital pole	Head injury

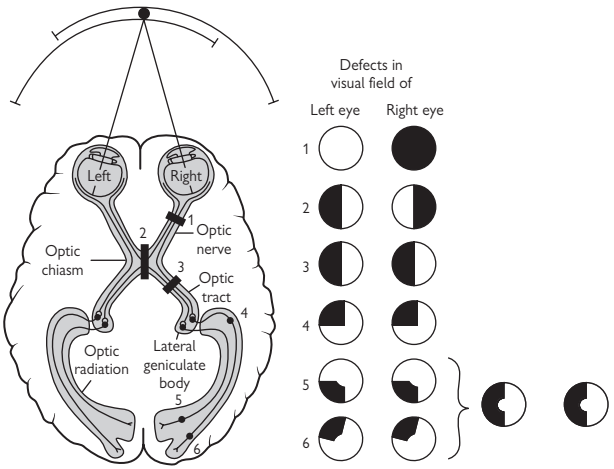

Figure 1.2 Diagram of visual field defects. 1. Unilateral blindness; 2. Bitemporal hemianopia; 3. Homonymous hemianopia; 4. Superior quadrantanopia; 5, 6. Inferior and superior quadrantanopias with macular sparing. Based on Figure 4.4 from An Introduction to the Biology of Vision, Cambridge University Press.

Pupillary reactions (cranial nerves II and III)

- Test reaction to light: direct and consensual with a bright pen light; ophthalmoscope light not strong enough (see Table 1.2).
- Accommodation reflex is observed by watching the pupil as gaze is shifted from a distant object to a near object.
- Relative afferent pupillary defect (Marcus–Gunn pupil) results from optic nerve dysfunction or, if extensive, retinal disease. Detected by the "swinging flashlight test"—a bright light is quickly moved back and forth between the eyes. The affected eye dilates rather than constricts when the light is swung to it because less light is perceived by the damaged pathway.

Funduscopy with the direct ophthalmoscope

- Reduce the ambient light in the room as much as possible.
- Turn on the ophthalmoscope and adjust the size of the light to approximate the size of the pupil.
- Look for the red reflex and move in to focus on the optic disc.
- Assess disc color for pallor.

Funduscopic findings

- Pigmented temporal crescent seen in myopes.
- Eighty percent of normal discs will have venous pulsation. May be elicited by gentle eyeball pressure.
- Disc edema (called "papilledema" if secondary to increased intracranial pressure)

Table 1.2 Pupillary abnormalities

Abnormality	Pupils	Other features	Tests
Oculomotor (cranial nerve III) palsy	Dilated; no response to light or accommodation	Weakness: MR, IO, IR, SR. Ptosis (complete/partial)	—
Horner syndrome (miosis, ptosis, anhidrosis)	Constricted pupil; reacts to light and accommodation	Partial ptosis, also upside-down ptosis (lower lid elevation), anhidrosis	10% cocaine dilates normal pupil but not sympathetic denervated one. 1% hydroxyamphetamine dilates pupil in first- or second-order neuron damage
Argyll Robertson pupil	Small, horizontally elongated pupil. Response to accommodation but not to light	Syphilis, diabetes, Parinaud syndrome	—
Tonic pupil (Adie)	Dilated pupil constricts slowly to accommodation. Unreactive to light but will constrict on prolonged and intense illumination. Vermiform movements visible on slit lamp	Generalized areflexia = Holmes–Adie syndrome	0.125% pilocarpine constricts pupil

IO, inferior oblique; IR, inferior rectus; MR, medical rectus; SR, superior rectus.

  - Hyperemia of disc margin
  - Blurring of margins
  - Raised optic disc
  - Engorged veins
  - Hemorrhages
  - Cotton wool spots and exudates
  - Retinal folds.
- Retinal abnormalities
  - Hard and soft exudates
  - Microaneurysms and new vessel formation
  - Pigmentary changes (bone spicules in retinitis pigmentosa).
- Macular changes (star, cherry red spot).
- Drusen or hyaline bodies are shiny bodies on the surface, near or buried in the disc elevating it and resembling papilledema.
- Medullated nerve fiber layer (pearly white) is myelin from the optic nerve that continues into the nerve fiber layer. May be confused with papilledema.

Cranial nerves III (oculomotor), IV (trochlear), and VI (abducens)

See Figure 1.3. Figure 1.4 shows the muscles innervated by cranial nerves III, IV, and VI.

Diplopia (see Table 1.3)

- Monocular diplopia may be functional, or due to refractive error, cataract, media opacity, macular disease, or a visual cortex disorder (bilateral).
- Horizontal diplopia is due to weakness of medial or lateral rectus.
- Oblique separation with one image slightly tilted is due to superior or inferior oblique weakness.
- Images are maximally separated when direction of gaze is toward the site of maximal action of the paretic muscle.
- The outer image comes from the paretic eye.
- If head tilt is present, it is in the direction of action of the affected muscle (e.g., a right IV palsy would be associated with the head down and the top of the head rotated to the left).

Eye movements: pursuits and saccades

- Fixation—observe the fixed eye for 30 seconds: horizontal square wave jerks are seen in cerebellar disease, progressive supranuclear palsy (PSP), and multiple system atrophy (MSA).
- Saccades (rapid conjugate eye movements) tested by asking the patient to fixate between two targets. Observe for speed of initiation (latency).
  - Undershoot = hypometria found in cerebellar disorders, PD, and Huntington disease (HD).
  - Overshoot = hypermetria caused by cerebellar dysfunction.
  - May help detect a subtle internuclear ophthalmoplegia (INO). In a partial lesion, there will be slowing of adduction ipsilateral to the lesion and nystagmus in contralateral abducting eye. In complete lesion, adduction is absent. INO is caused by a lesion of the medial longitudinal fasciculus, usually from demyelination or stroke (see Fig. 1.5).

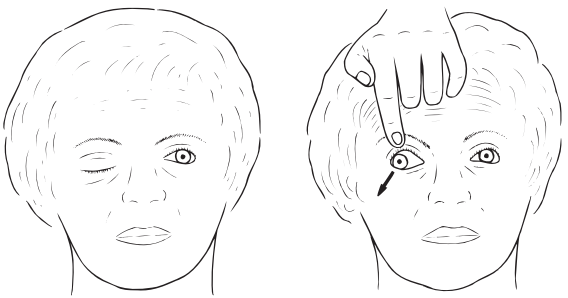

Figure 1.3 Paresis of the oculmotor nerve. Ptosis due to paresis of the levator palpebrae muscle. The right eye is abducted and infraducted due to the unopposed actions of the lateral rectus and superior oblique muscles.

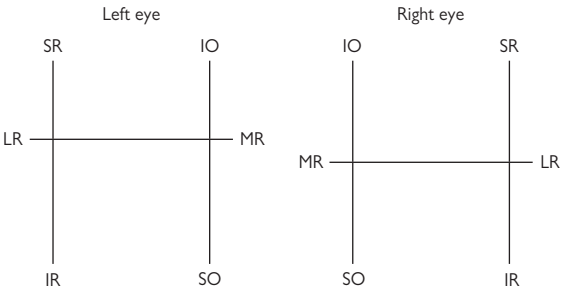

Figure 1.4 Diagram showing muscles innervated by cranial nerves III, IV, and VI. Cranial nerve III: medical rectus (MR); inferior oblique (IO); superior rectus (SR); inferior rectus (IR). Also levator palpebrae. Cranial nerve IV: superior oblique (SO). Cranial nerve VI: lateral rectus (LR).

Table 1.3 Clinical features to distinguish cranial neuropathies and internuclear ophthalmoplegia

	III	IV	VI	Internuclear ophthalmoplegia
Diplopia	Oblique	Vertical	Horizontal	Horizontal
Diplopia worse with	Near target	Looking down	Far target	Near target
Head tilt	Up and in	Head down and rotated away from lesion	Toward lesion	None
Other features	Large, unreactive pupil			No diplopia in primary gaze. Convergence may be spared.

- Smooth pursuit. Test horizontal and vertical movements by tracking a target keeping the head still. Broken pursuit nonspecific sign due to cerebellar disease, drugs, e.g., anticonvulsants and sedatives. If only in one direction indicates posterior cortical lesion ipsilateral to the direction of broken pursuit.

Nystagmus

- Involuntary oscillation is initiated by a slow drift of the eye. If followed by a corrective fast phase = jerk nystagmus; if both phases have equal velocity = pendular nystagmus. Direction of nystagmus described by fast phase.

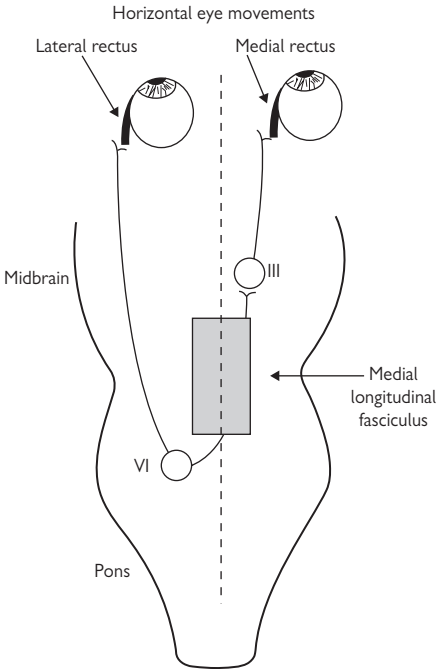

Figure 1.5 Horizontal eye movements. VI is activated by the paramedian pontine reticular formation (PPRF), which in turn received input from the contralateral frontal eye fields.

- Jerk nystagmus caused by vestibular system imbalance, either peripheral vestibular structures (labyrinth, vestibular nerve) or central vestibular structures (brainstem, cerebellum). See Table 1.4.

Peripheral vestibular patterns

- Acute vestibular lesion
  - Spontaneous unidirectional horizontal > torsional nystagmus
  - Increased velocity of nystagmus with gaze in the direction of the fast phase
  - Suppressed with fixation
  - Does not change direction
  - Rarely mimicked by lesion in central vestibular structures

Positionally triggered nystagmus

- Posterior canal benign paroxysmal positional vertigo (BPPV)
  - Burst of upbeat torsional nystagmus with Dix-Hallpike test
  - Duration of nystagmus <30 seconds

Table 1.4 Features of acute peripheral and central vestibular nystagmus

Acute peripheral	Central
Unidirectional fast phase beating away from affected labyrinth	Uni- or multidirectional
Horizontal >> torsional pattern	Pure vertical (usually downbeating) or pure torsional
Associated with severe vertigo, vomiting, nausea	Mild symptoms. Other neurological signs are generally present, e.g., impaired smooth pursuit, ataxia, disconjugate eye movements, pyramidal signs
Amplitude increases with gaze toward the direction of the fast phase, then decreases in opposite direction (never changes direction)	May be gaze evoked
Suppressed by fixation (Frenzel goggles removes fixation)	No change with fixation

- Horizontal canal BPPV
  - Horizontal nystagmus triggered by head turns while in a supine position.
  - Duration can be as long as position held.
  - Direction of nystagmus can be toward or away from the direction of head turn.

Central vestibular patterns

- Downbeat nystagmus
  - Can be present in the primary position, with gaze or triggered by positionally testing
  - Due to disturbance of vestibulocerebellum caused by Arnold–Chiari malformation, cerebellar degeneration, drug toxicity, e.g., lithium
- Upbeat nystagmus
  - Generally present in primary position but can be brought out by gaze or positional testing
  - Less localizing than downbeat nystagmus—can occur with lesions of the paramedian medulla but also pontine or midbrain lesion
  - Causes: multiple sclerosis (MS), vascular, cerebellar degeneration
- Pure torsional nystagmus
  - Can be in primary gaze or triggered by positional testing
  - Generally localizes to the medulla
  - Common causes: syringobulbia, stroke, tumor
- Gaze-evoked nystagmus (GEN)
  - Only present on eccentric gaze not primary position
  - May be horizontal, upbeating on upgaze and/or down beating on downgaze
  - Bilateral horizontal GEN due to cerebellar and brainstem disorders, drugs, alcohol, diffuse metabolic disorders

Cranial nerves V and VII–XII

Cranial nerve V (trigeminal)

Sensory via three divisions (ophthalmic V^1, maxillary V^2, mandibular V^3) (see Fig. 1.6)

- Sensation but not taste to anterior two-thirds of the tongue also supplied by trigeminal nerve.
- Motor fibers to muscles of mastication (temporalis, masseter, and pterygoids via mandibular division)
- Jaw deviates to side of weak pterygoid muscle.
- Corneal reflex has a consensual component. Useful in the presence of an ipsilateral facial palsy.
- Jaw jerk—if brisk indicates pathology above midbrain level.

Cranial nerve VII (facial)

- Supplies the muscles of facial expression and taste to anterior two-thirds of the tongue (via corda tympani branch).
- Lower motor neuron facial palsies result in complete ipsilateral facial weakness.
- The upper face is bilaterally innervated—frontalis and to a lesser extent orbicularis oculi are spared in upper motor neuron palsies.

Cranial nerve VIII (vestibulocochlear nerve)

- Two divisions:
  - Cochlear (hearing)
  - Vestibular (balance)
- Hearing is crudely tested by whispering numbers in one ear while blocking the other.
- Rinne test—Hold 256 Hz tuning fork base on mastoid. Wait until sound disappears, and then hold tines in the air next to the ear.
  - Normal or sensorineural deafness—air conduction is louder than bone conduction.
  - Conductive deafness—bone conduction is louder than air conduction.
- Weber test—tuning fork placed in middle of forehead.
  - Unilateral conductive deafness—louder to the ipsilateral side
  - Sensorineural deafness—louder to contralateral side

Cranial nerve IX (glossopharnygeal nerve)

- Taste fibers from posterior third of the tongue
- General sensation tympanic membrane, mucous membranes from posterior pharynx, tonsils, and soft palate
- Afferent part of the gag reflex

Cranial nerve X (vagus nerve)

- Motor fibers innervate the striated muscles of palate, pharynx, and larynx.
- Soft palate observed as patient says "aahh." The uvula deviates away from side of lesion.

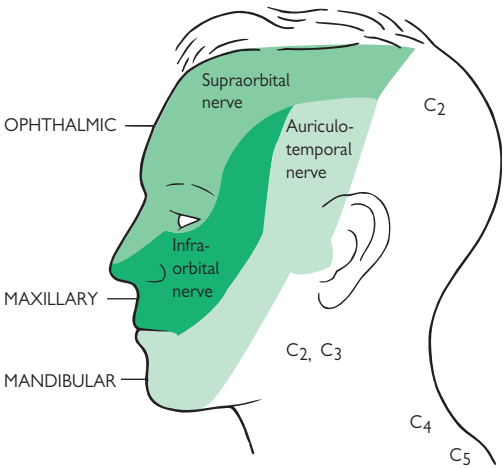

Figure 1.6 The cutaneous distribution of the three branches of the trigeminal nerve. (Reproduced with permission from *The Central Nervous System* by Per Brodal.)

- Lesions of recurrent laryngeal branch cause ipsilateral vocal cord paralysis with dysphonia and a weak cough.
- Parasympathetic autonomic fibers travel in the vagus nerve to the respiratory, gastrointestinal (GI), and cardiovascular systems.

Cranial nerve XI (spinal accessory nerve)

- Innervation to sternocleidomastoid (SCM) and trapezius.
- SCM (supplied by ipsilateral hemisphere) assessed by asking patient to twist the head against resistance and palpate contralateral SCM.
- Trapezius assessed by shoulder shrug and palpating muscle.

Cranial XII (hypoglossal nerve)

- Observe for fasciculations. Observe with tongue inside the mouth.
- Tongue strength assessed by asking patient to push inside the mouth against cheek.
- Tongue movement dexterity assessed by asking patient to move tongue side to side. Slowness without wasting suggests spasticity.
- In hypoglossal lesions, tongue deviated to the side of the lesion.

Motor examination

Ideally, patient should be stripped to underclothes.

General points

- Document hand dominance.
- Look for wasting—first dorsal interosseus muscle easiest (ulnar).
- Examine scapular muscles (winging of the scapula due to lesions of long thoracic nerve).
- Palpate extensor digitorum brevis (EDB) on the foot. This muscle is often atrophic in neurogenic conditions.
- Observe for fasciculations—may need to spend a few minutes in good light.
- Have patient hold arms outstretched with palms up and eyes closed.
  - Pronator drift indicates mild pyramidal weakness.
  - Pseudoathetosis (involuntary movements of fingers) indicates loss of position sense.
  - Postural tremor may be caused by essential tremor, demyelinating neuropathy, or drugs (sodium valproate, steroids).
- Have the patient rotate arms around each other with elbows flexed. If one arm orbits around the other, the arm that is moving less may be weaker.

Tone

Spastic (pyramidal) assessed by the following:

- Upper limbs:
  - Rapid flexion/extension movement at the elbow (clasp knife)
  - Supinator catch (rapid supination movement at wrist)
  - Hoffman sign (rapid flexion at DIP joint of middle finger results in brisk flexion movements at other fingers)—positive in upper motor lesions
- Lower limbs:
  - Brisk flexion of the knee when legs extended results in a catch if tone increased.
  - Test for clonus at ankles.
  - Have the patient lie on back and lift thigh from bed. In normal or low tone, the heel will drag on the bed. If tone is increased, the heel will elevate.

Extrapyramidal increase in tone assessed by the following:

- By slow flexion/extension movements at the wrist
- May be enhanced by synkinesia (ask patient to move contralateral limb)

Muscle strength

All that is required is maximal strength for one second—useful in patients with "giveway weakness." Table 1.5 gives the muscles to be tested, and Table 1.6 gives a grading system to evaluate the results.

Coordination

- Finger tapping—have the patient tap the crease of the thumb with the tip of the index finger and observe for speed, regularity of rhythm, and accuracy.

Table 1.5 Important myotomes

Muscle*	Roots	Nerve	Action
Trapezius	C3–C4	Spinal accessory	Shrug shoulder
Rhomboids	C4–**C5**	Dorsal scapular	Brace shoulders back
Supraspinatus	**C5**–C6	Suprascapular	Abduct shoulder 15°
Deltoid	C5–C6	Axillary	Abduct shoulder 15°–90°
Infraspinatus	**C5**–C6	Suprascapular	External rotation of arm
Biceps	C5–C6	Musculocutaneous	Flex forearm
Triceps	C6–**C7**–C8	Radial	Extend forearm
Extensor carpi radialis	**C6**–C7	Radial	Extend wrist
Extensor digitorum	**C7**–C8	Posterior Interosseous	Extend digits 3–5
Extensor indicis	C7–**C8**	Posterior interosseous	Extend index finger
FDP II and III	C7–C8	Median	Flex DIPJ
FDP IV and V	**C8**–T1	Ulnar	Flex DIPJ
FDS	C7–C8–T1	Median	Flex PIPJ
APB	C8–T1	Median	Abduct thumb
OP	C8–T1	Median	Thumb to 5th finger
Flexor pollicis longus	C7–**C8**	Anterior interosseous	Flex thumb
ADM	C8–T1	Ulnar	Abduct 5th finger
FDIH	C8–T1	Ulnar	Abduct index finger
Iliopsoas	L2–L3	Femoral	Flex hip
Adductor longus	L2–L3–L4	Obturator	Adduct hip
Gluteus maximus	L5–**S1**–S2	Inferior gluteal	Extend hip
Quadriceps	L2–L3–**L4**	Femoral	Extend knee
Hamstrings	L5–S1	Sciatic	Flex knee
Tibialis anterior	L4–**L5**	Deep peroneal	Dorsiflex ankle
Gastrocnemius	L5–S1–S2	Tibial	Plantarflex ankle
Tibialis posterior	**L5**–S1	Tibial	Invert foot
EHL	**L5**–S1	Deep peroneal	Dorsiflex great toe
EDB	**L5**–S1	Deep peroneal	Extend toes
Peroneus longus	**L5**–S1	Superficial peroneal	Evert foot

*Muscles in bold font are essential in a basic neurological examination.

ADM, abductor digiti minimi; APB, abductor pollicis brevis; DIPJ, distal interphalangeal joint; EDB, extensor digitorum brevis; EHL, extensor hallucis longus; FDIH, first dorsal interosseous of the hand; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; OP, opponens pollicis; PIPJ, proximal interphalangeal joint.

Table 1.6 MRC grading system for muscle strength

MRC grade	Observed muscle power
0	No movement
1	Flicker of movement
2	Movement with gravity eliminated
3	Movement against gravity
4, 4+, or 4 –	Able to overcome some resistance
5	Normal power

MRC, Medical Research Council.

- Rapid alternating hand movements—have the patient pronate and supinate the hand on a stable surface. Observe speed, accuracy, and rhythm. Dysdiadokinesia is the inability to perform this action normally.
- Finger-to-nose testing—have the patient move his or her finger back and forth between his or her nose and your finger. Hold your finger far enough away so the patient has to extend the arm fully. Observe for accuracy, kinetic tremor (tremor throughout movement), and intention tremor (tremor that increases in amplitude as the target is approached).
- Heel-to-shin testing—have the patient move his or her heel up and down his or her shin. Best done with the patient supine. Observe for accuracy and tremor.

Sensory testing

- Test the integrity of the afferent pathways. Map out abnormality to determine if it is in the distribution of a single nerve or dermatome, a length-dependent pattern, a spinal level, or if there is hemianesthesia suggesting a brain or brainstem localization.
- Primary sensory modalities
  - Light touch—this is best done with a cotton wisp.
  - Pain—use a safety pin and ask the patient to tell you if you are applying pressure with the sharp end or the dull end.
  - Temperature—a cold tuning fork should be felt equally in all four extremities.
  - Vibration—hold a 128-Hz tuning fork firmly on the patient's distal phalanx and let the vibration fade until the patient can no longer detect it.
  - Proprioception (joint position sense)—hold the medial and lateral aspects of the distal phalanx and ask the patient to tell you if you are moving the digit up or down. Most patients can identify changes of just a few degrees. (Note: The Romberg test is also a means of measuring position sense.)
- Discriminative sensory functions—all tested with the patient's eyes closed.
  - Extinction—ask the patient to tell you whether you are touching the extremities on the left, the right, or both.

Table 1.7 Deep tendon reflexes

Reflex	Nerve	Root
Biceps	Musculocutaneous	C5/6
Brachioradialis	Radial	C5/6
Triceps	Radial	C7
Finger flexors	Median/ulnar	C8
Knee	Femoral	L4
Ankle	Tibial	S1

- Graphesthesia—ask a blindfolded patient to identify a number drawn on his or her index finger with a ballpoint pen.
- Stereognosis—ask the patient to identify a small object (e.g., coin, key, paperclip, guitar pick) placed in his or her hand.

Deep and superficial tendon reflexes (see Table 1.7)

Deep tendon reflexes

- The deep tendon reflexes are graded from 0 (absent), trace (present with reinforcement), 1+ (depressed), 2+ (normal), 3+ (increased), or 4+ (sustained clonus).
- Reinforcement can be obtained by jaw clenching or Jendrassik maneuver (patient links hands and pulls).
- Deep tendon reflexes may also be inverted—the tested reflex is absent, but there is spread to a lower level. This indicates a lower motor neuron lesion at the level of the reflex but an upper motor neuron lesion below (most common at C5/C6).

Main superficial reflexes

- Abdominal (upperT8/9; lowerT10/11)—absent in some upper motor neuron lesions
- Cremasteric (L1/2)—elicited by stroking inner thigh with reflex ipsilateral testicular elevation
- Anal (S4/5)—scratch anal margin with reflex contraction visible

Gait examination

- Casual gait—observe how far apart the feet are while walking.
- Heel walk (tibialis anterior) and toe walk (gastrocnemius) are good for assessing subtle weakness in these muscles.
- Tandem gait—have the patient walk heel to toe, as if on a tightrope. This is a more sensitive way to assess for balance difficulties.
- Romberg sign. The patient stands with eyes closed and feet together. Falling without catching oneself suggests disturbance of proprioception. Useful in nonorganic disorders.

The various gait disturbances encountered in clinical practice are shown in Table 1.8.

Table 1.8 Gait disturbances encountered in clinical practice

Gait disturbance	Description	Common causes
Gait apraxia	Small shuffling steps—"marche à petits pas"; difficulty in starting to walk; cycling on bed significantly better	Small vessel disease, hydrocephalus
Parkinsonian	Shuffling; loss of arm swing, festination, en bloc turns	Parkinson disease, dementia with Lewy Bodies, PSP, MSA
Spastic paraparesis	Stiff scissoring gait	Cord lesion, parasagittal lesion
Myopathic	Waddling	Myopathic, dystrophic disorders
Foot drop	Foot slapping, "steppage gait"	Peroneal neuropathy, radiculopathy, rarely UMN
Cerebellar ataxia	Wide-based; "drunken"	Any cerebellar pathology
Sensory ataxia	Wide-based; foot slapping; deteriorates with eye closure	Neuropathy, subacute combined degermation of cord, posterior column disorders, e.g., MS

MS, multiple sclerosis; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; UMN, upper motor neuron syndrome.

Bedside cognitive testing, including language

There is no point in attempting a cognitive assessment in a patient who is drowsy or uncooperative.

1 Alertness Record the level of wakefulness and reactivity.

2 Orientation

- Time (time of day; day of the week, month, and year). Disorientation in time common in delirium, moderate dementia, and amnestic syndromes.
- Place (building, town, county, country).
- Person (name, age, date of birth). Dysphasic patients may appear confused due to an inability to understand or express themselves.

3 Attention and concentration

- Count backwards from 20.
- List the months of the year backward.

- Digit span. Ask patient to repeat string of increasing digits—two trials at each level. Record highest level at which either trial is correct, e.g.,

3	4	8		
4	7	9		
2	3	6	7	
1	4	5	9	
2	7	9	5	6
1	8	7	2	3

Normal 6 ± 1

4 Memory

Anterograde memory

- Name and address, e.g., John Green, 157, Church Lane, Ann Arbor, MI
- Assess immediate recall and after 5 minutes

Retrograde memory

- Recent world events—sports, celebrity news or scandals, president and vice president
- Autobiographical memory—parents, childhood events

5 Frontal executive function (frontal lobe)

Initiation—verbal fluency test

- Ask patient to generate as many words as possible in 1 minute beginning with the letter F, A, or S, excluding names of people or places. Normal: 15 depending on age and intellect.
- Name as many animals or fruits in 1 minute. >20, normal; <10 abnormal.

Abstract thought

Interpretation of proverbs (frontal lobe disorders result in concrete interpretations), e.g., "a stitch in time saves nine"; "too many cooks spoil the broth."

Cognitive estimates

Frontal patients give bizarre and illogical answers to questions like the following:

- What is the height of an average American woman?
- What is the population of Milwaukee?
- How many bison are there in Michigan?

Alternating hand movements

- With arms out, fingers of one hand extended; the other with fist clenched. Reverse positions rhythmically (see Fig. 1.7).
- Luria three-step test (see Fig. 1.8). Difficulties with complex motor movements associated with left frontal lesions.

6 Dominant (usually left) hemisphere function

Language

Aphasia (Table 1.9) and dysphasia are impairments of language function. Dysarthria is the abnormal motor production of speech.

- Spontaneous speech assessed during conversation and description of a picture.

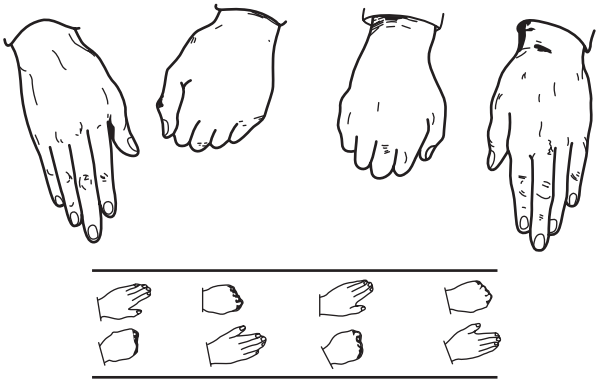

Figure 1.7 Alternating hand movements test. The hand positions (above) and the sequence of movements to the patient (below) are shown.

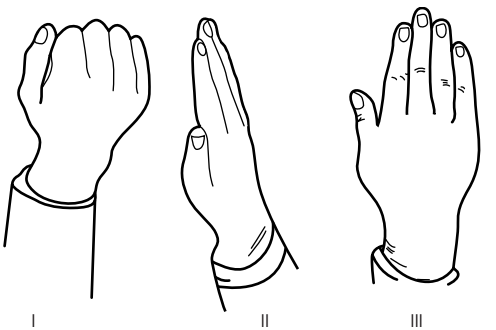

Figure 1.8 Luria three-step test sequence of hand positions (first—edge—palm) is shown.

  - Articulation (abnormal in bulbar, cerebellar, and basal ganglia disorders)
  - Fluency—in nonfluent speech reduced rate of word production and short phrases
  - Grammar—lack of pronouns, prepositions, and errors of tense. Correlates with nonfluent language.
  - Paraphasic errors—word substitution, e.g., black for blank (similar sounding = phonemic) or apple for pear (meaning-based = semantic)
  - Prosody—loss of intonation, pitch, and stress occur in right hemisphere lesions but also in nonfluent speech and in articulatory disorders
- Naming. Record 10 items—a mixture of common and uncommon objects, e.g., pen, watch, sleeve, buckle, lapel.

Table 1.9 Types of aphasias and characteristics

Type of aphasia	Fluency	Repetition	Comprehension	Naming
Nonfluent (Broca)	–	–	+	–
Fluent (Wernicke)	+	–	–	–
Transcortical motor	–	+	+	–
Transcortical sensory	+	+	–	–
Mixed transcortical	–	+	–	–
Conduction	+	–	+	+
Global	–	–	–	–

- Comprehension:
  - Single words—point to objects in the room, e.g., door, ceiling
  - Complex instructions—e.g., "Pick up the piece of paper, fold it in half, and give it to me"
  - Conceptual—e.g.,"What is the color of a banana?" "What is the name of item in the kitchen that enables you to cut?"
- Repetition, e.g., "A koala is not really a bear," "Shiver me timbers"
- Reading a passage (see example in Box 1.1) usually parallels spoken language problems. Occasionally alexia can occur without aphasia.
- Writing—ask patient to write any novel sentence. Dictate a sentence, e.g., "The cat sat on the mat."

Calculation *Simple arithmetic (addition, subtraction).*

Praxis skills First to command and, if not possible, then by imitation "show me how you would":

- Blow a kiss (buccofacial)
- Wave goodbye (limb gestures)
- Hammer a nail (object use)

7 Nondominant (usually right) hemisphere function

Neglect

- Sensory neglect: patient ignores visual, tactile, and auditory stimuli from left side.
- Sensory extinction: patient responds to visual or tactile stimulus from each side separately, but when bilateral stimuli presented ignores neglected side.
- Hemispatial neglect: in drawing a clock face, the left side of clock is omitted. Often all numbers are drawn on the right hemisphere of the clock.
- Dressing apraxia: patient unable to dress, e.g., shirt inside out.
- Constructional ability. Copy shapes, e.g., overlapping pentagons (see Fig. 1.9).
- Prosopagnosia: patient demonstrates impaired facial recognition.

Box 1.1 Example of passage for reading

Most visitors to our park are under the impression that the best way to prevent being injured in a stampede is simply to avoid large herds of grazing animals. Unfortunately, smaller groups of animals may be just as dangerous. As few as three bison, if startled or upset, could trample upon a traveler and cause serious harm. While you are here, feel free to hike the park's many paths and enjoy the rustic beauty of the Michigan countryside. However, if you see a group of three or more bison, I would encourage you to back away slowly.

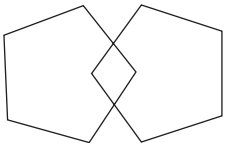

Figure 1.9 Overlapping pentagons from the mini-mental state examination (MMSE).

The mini-mental state examination (MMSE)

Commonly used bedside test (see Table 1.10).[1] Caveats include the following:

- Take into account age, education, and culture.
- Insensitive to focal deficits, especially frontal lobe
- Cut-off score is 24/30, but patients with superior background IQ may perform well despite significant cognitive impairment.
- The MMSE tests multiple areas of cognition but does not adequately evaluate executive function (judgment, insight). The Montreal Cognitive Assessment (MoCA) is probably a better screening tool for dementia. However, the MMSE is used more commonly, so the scores may have more meaning to other practitioners who see the patient.

1 Folstein, MF, Folstein, S, McHugh, PR (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res* 12:189–198.

Table 1.10 The mini-mental state examination (MMSE)*

Test	Score per Item	Maximum score/test
Orientation		
Year, month, day, date, season	1	5
Country, county, town, hospital,† ward/room	1	5
Registration		
Examiner names three objects (e.g., ball, pen, key). Patient repeats each item.	1	3
Attention		
Ask patient to start with 100 and subtract 7. Stop after five subtractions, e.g., 100, 93, 86, 79, 72, 65. *or* Ask patient to spell five-letter word backward, e.g., "world." Score number of letters in correct order.	1	5
Recall	1	3
Ask for the three words you asked patient to number in "Registration" test.		
Language		
Naming: point to object and ask patient to name it, e.g., watch, tie.	1	2
Repetition	1	1
Ask patient to repeat sentence after you (only one trial allowed), e.g., "No ifs, ands, or buts."		
Three-stage command	1	3
E.g., "Take this paper, fold it into half, and give it to me." Score 1 point for each stage of command correctly executed.		
Reading	1	1
Ask patient to read a command on paper, e.g., "Close your eyes," and to execute it.		
Writing		
Ask patient to write a sentence. To score 1 it must be sensible and must contain a noun and a verb.	1	1
Copying		
Copy picture of intersecting pentagons (Fig. 1.8). To score 1, all 10 angles must be present and two must intersect.	1	1
Maximum possible score		30

* No half-points are given in the MMSE.

† Home or hospital depending on location of the test.

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Chapter 2

Neuroanatomy

Zachary London, MD

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Innervation of the lower limbs *44*

Neuroanatomical figures

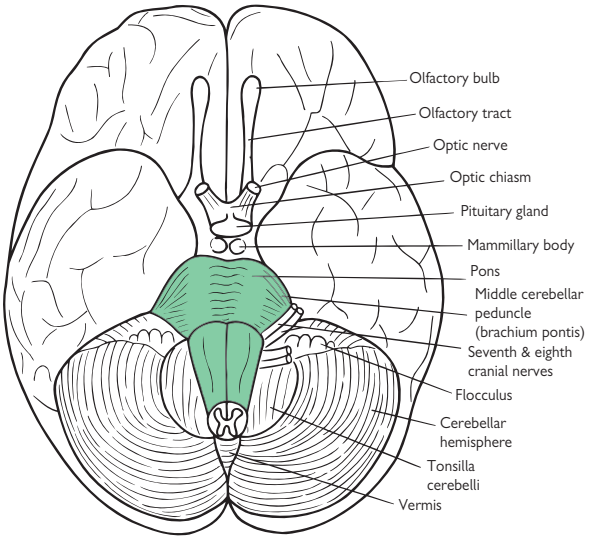

Figure 2.1 The basal aspect of the brain. (Reproduced with permission from *The Central Nervous System* by Per Brodal.)

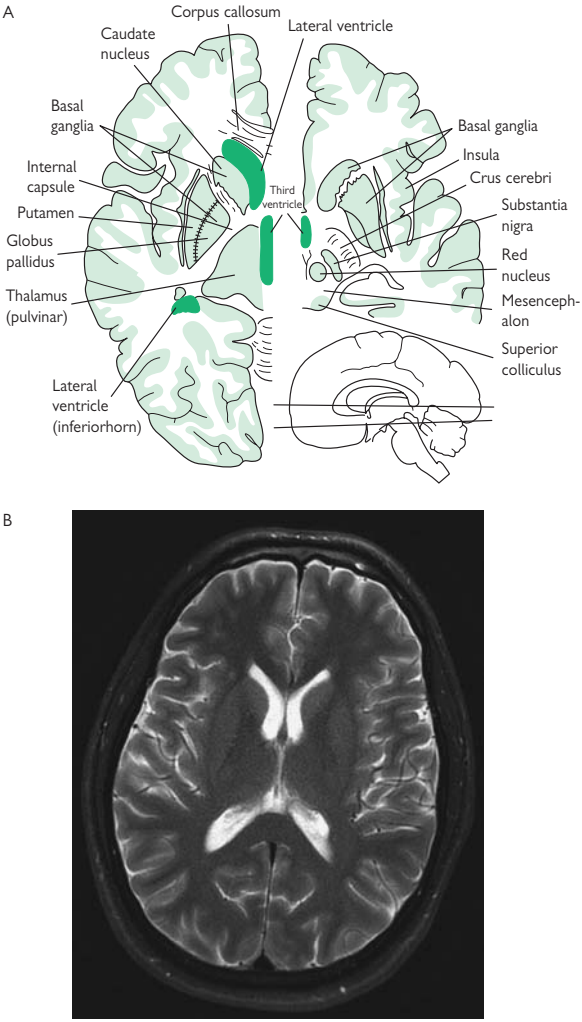

Figure 2.2 The cerebral hemispheres in horizontal sections. A: Drawings of two sections at slightly different levels. B: Magnetic resonance image (MRI), which corresponds closlely to the left level in A. (Reproduced with permission from *The Central Nervous System* by Per Brodal.)

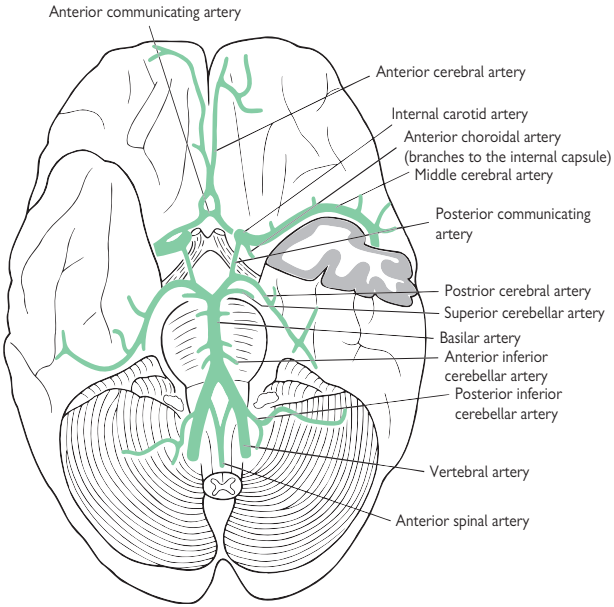

Figure 2.3 The main arteries of the brain. (Reproduced with permission from *The Central Nervous System* by Per Brodal.)

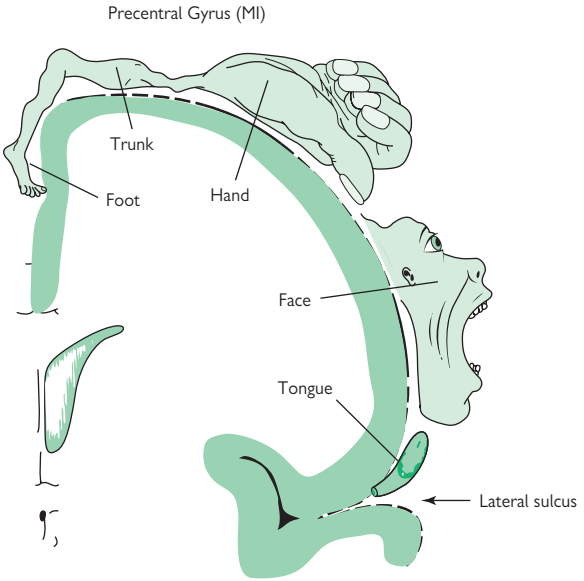

Figure 2.4 The motor homunculus or cortical representations of motor neurons. (Reproduced with permission from *The Central Nervous System* by Per Brodal.)

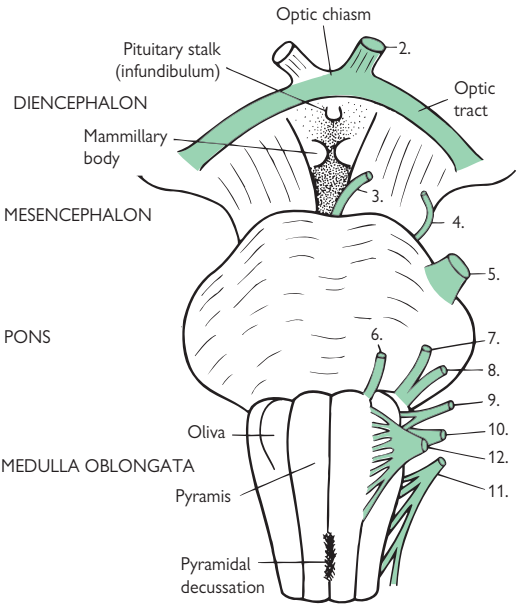

Figure 2.5 The cranial nerves as seen from the ventral side of the brainstem. The numbers in this figure refer to the corresponding cranial nerves. (Reproduced with permission from *The Central Nervous System* by Per Brodal.)

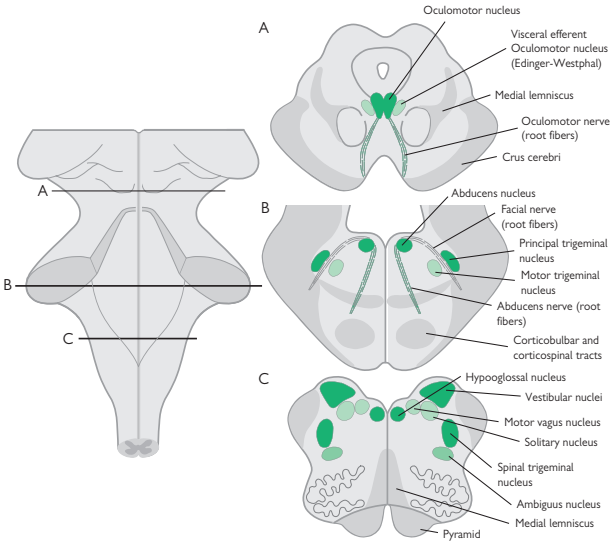

Figure 2.6 Position of cranial nerves at three levels of the brainstem: (A) mesencephalon, (B) pons, (C) medulla oblongata. (Reproduced with permission from *The Central Nervous System* by Per Brodal.)

Dermatomes of the upper and lower limbs

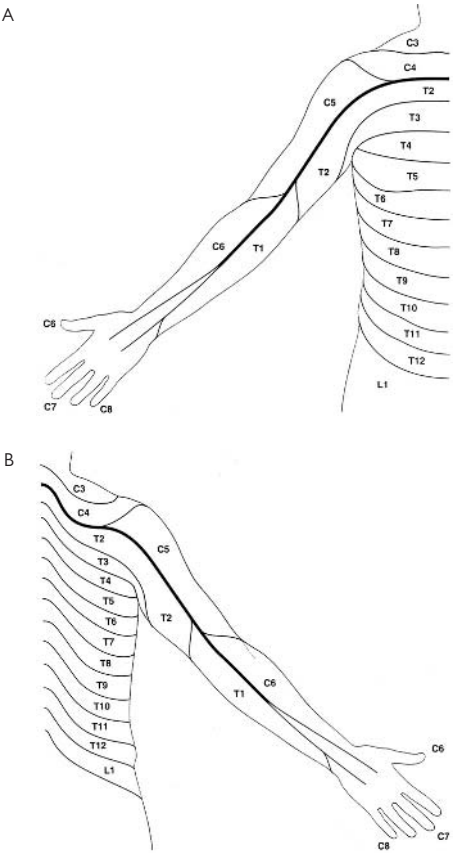

Figure 2.7 Approximate distribution of dermatomes: (A) on the anterior aspect of the upper limb; (B) on the posterior aspect of the upper limb.

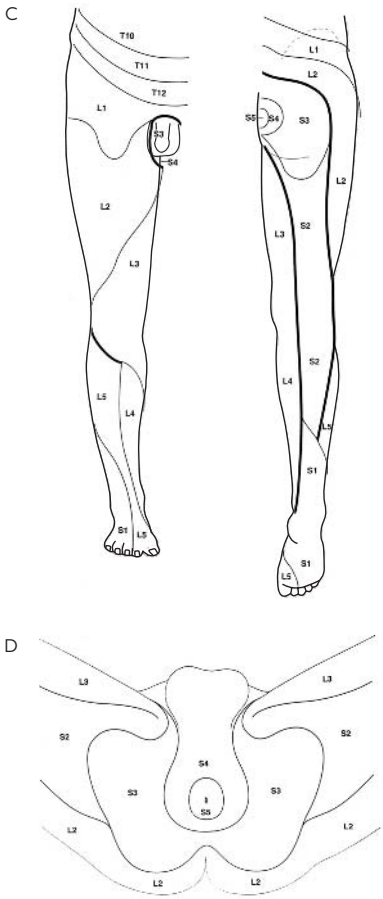

Figure 2.7 (*Contd.*) Approximate distribution of dermatomes: (C) on the lower limb; (D) on the perineum. (Reprinted from *Aids to the Examination of the Peripheral Nervous System*, 4th ed. [2000], pp. 56–59, with permission from Elsevier.)

Innervation of the upper limbs

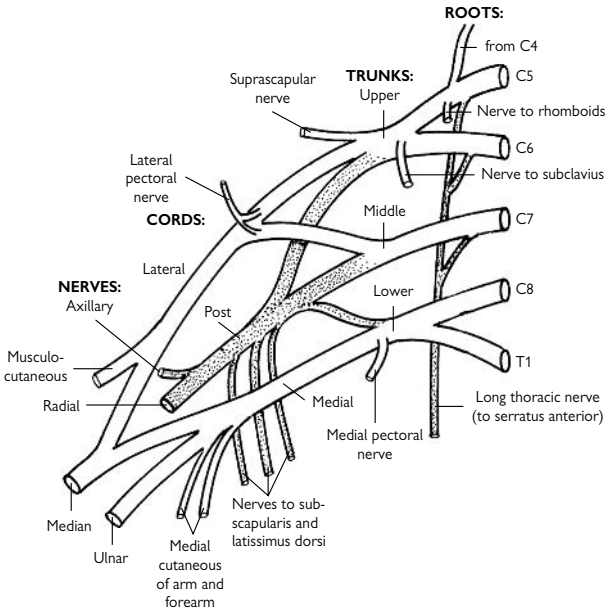

Figure 2.8 Brachial plexus: schematic diagram of trunks, cords, and branches. (Reproduced with permission from MacKinnon, P, Morris, J [2005]. *Oxford Textbook of Functional Anatomy*, Vol. 1, 2nd ed., Oxford, England: Oxford University Press.)

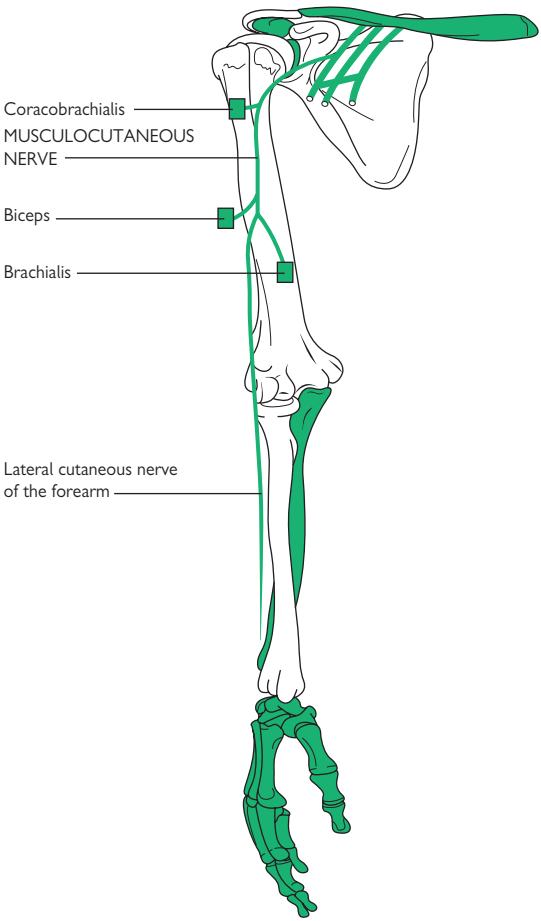

Figure 2.9 The musculocutaneous nerve, its major cutaneous branch and the muscles it supplies. (From *Aids to the Examination of the Peripheral Nervous System*, 4th ed., W.B. Saunders, On behalf of the guarantors of *Brain*.)

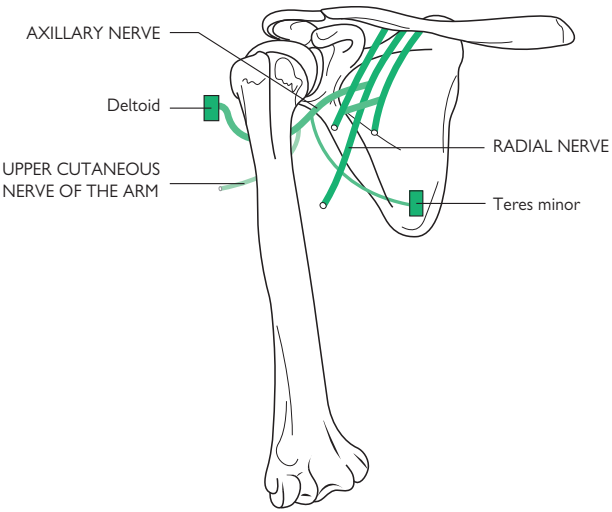

Figure 2.10 The axillary nerve, its major cutaneous branch, and the muscles that it supplies. (From *Aids to the Examination of the Peripheral Nervous System*, 4th ed., W.B. Saunders, On behalf of the guarantors of *Brain*.)

Figure 2.11 Cutaneous sensory distribution of the axillary nerve.

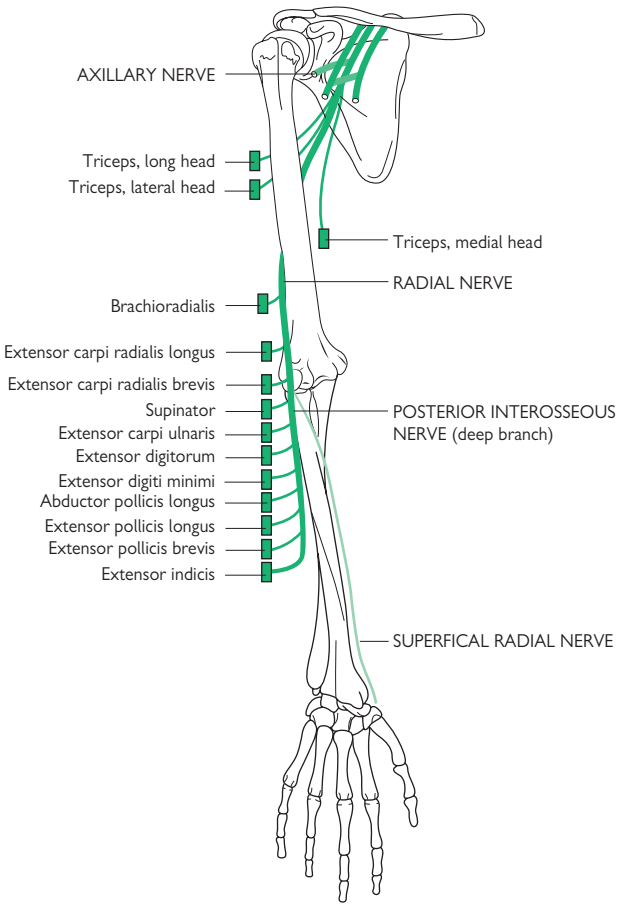

Figure 2.12 The radial nerve, its major cutaneous branch, and the muscles that it supplies. (From *Aids to the Examination of the Peripheral Nervous System*, 4th ed., W.B. Saunders, On behalf of the guarantors of *Brain*.)

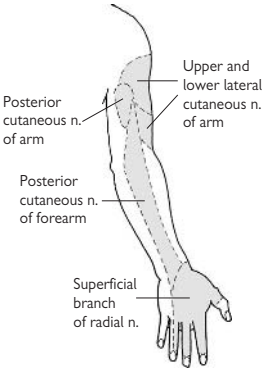

Figure 2.13 Cutaneous distribution of radial sensory branches.

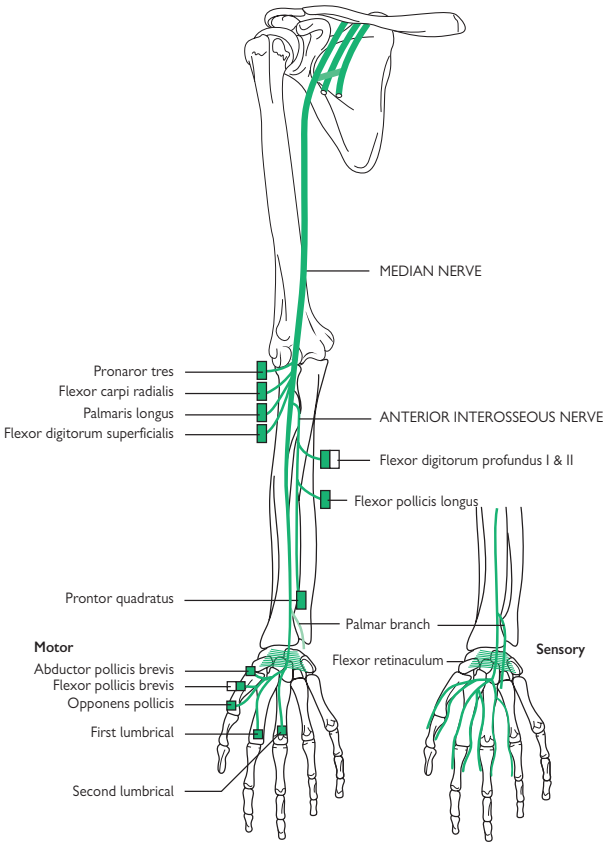

Figure 2.14 The median nerve, its cutaneous branches, and the muscles that it supplies. (From *Aids to the Examination of the Peripheral Nervous System*, 4th ed., W.B. Saunders, On behalf of the guarantors of *Brain*.)

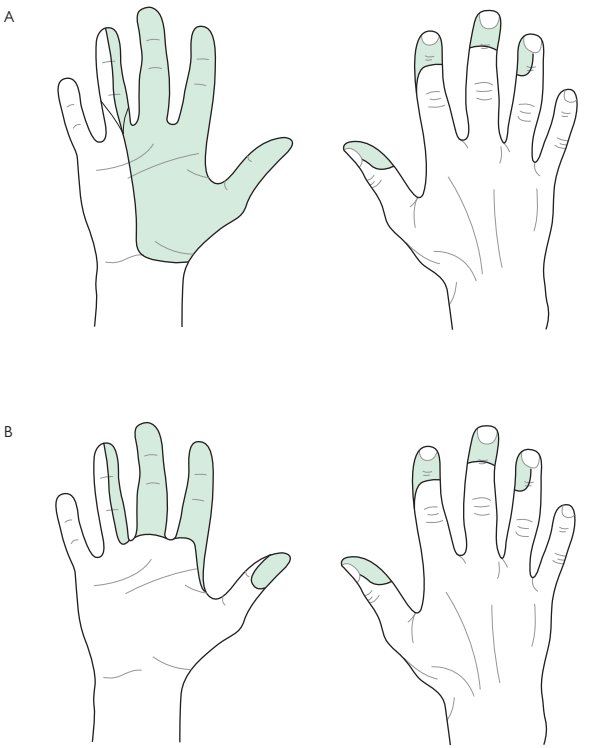

Figure 2.15 Cutaneous distribution of the median nerve with lesions in (A) the forearm and (B) the carpal tunnel. (From *Aids to the Examination of the Peripheral Nervous System*, 4th ed., W.B. Saunders, On behalf of the guarantors of *Brain*.)

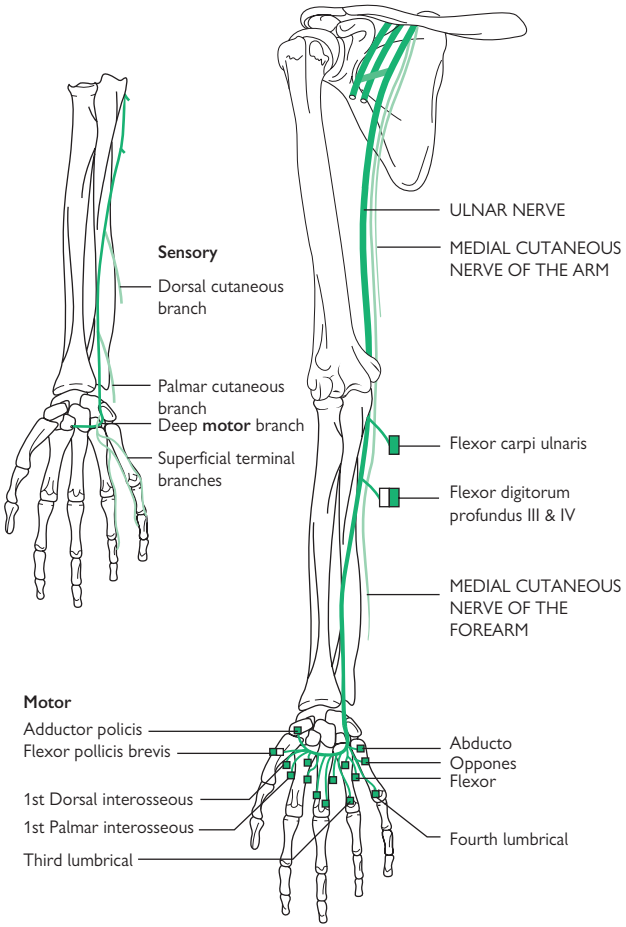

Figure 2.16 The ulnar nerve, its cutaneous branches, and the muscles that it supplies. (From *Aids to the Examination of the Peripheral Nervous System*, 4th ed., W.B. Saunders, On behalf of the guarantors of *Brain*.)

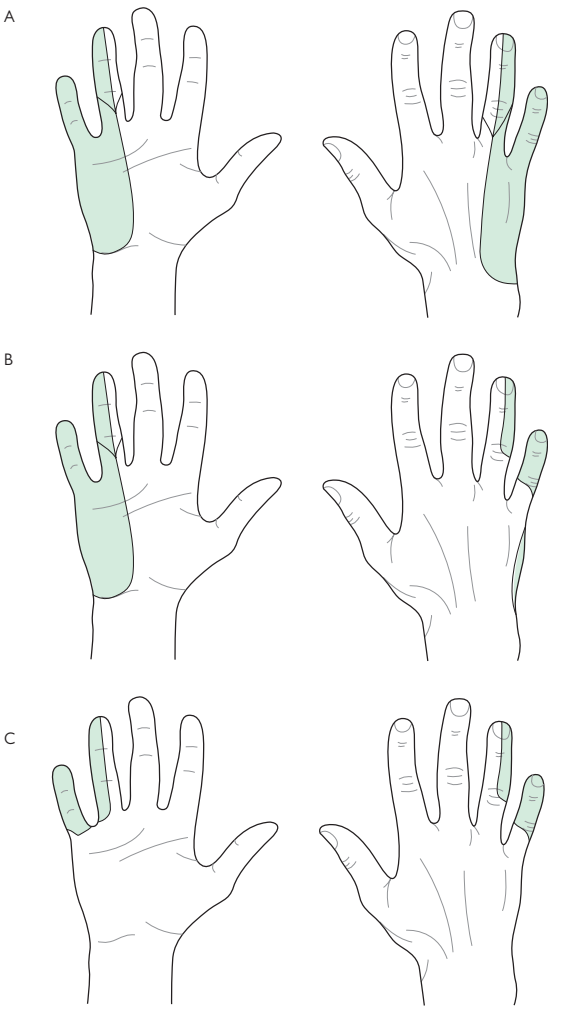

Figure 2.17 Cutaneous distribution of the ulnar nerve with lesions (A) above the origin of the dorsal ulnar cutaneous branch, (B) below the origin of the dorsal ulnar cutaneous branch and above the origin of the palmar branch, and (C) below the origin of the palmar branch. (From *Aids to the Examination of the Peripheral Nervous System*, 4th ed., W.B. Saunders, On behalf of the guarantors of *Brain*.)

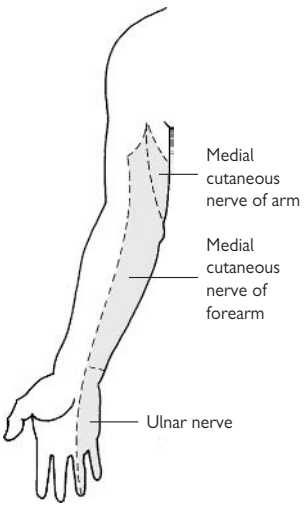

Figure 2.18 Distribution of medial cutaneous nerves of arm and forearm and of ulnar nerve. (Reproduced with permission from MacKinnon, P, Morris, J [2005]. *Oxford Textbook of Functional Anatomy*, Vol. 1, 2nd ed., Oxford, England: Oxford University Press.)

Innervation of the lower limbs

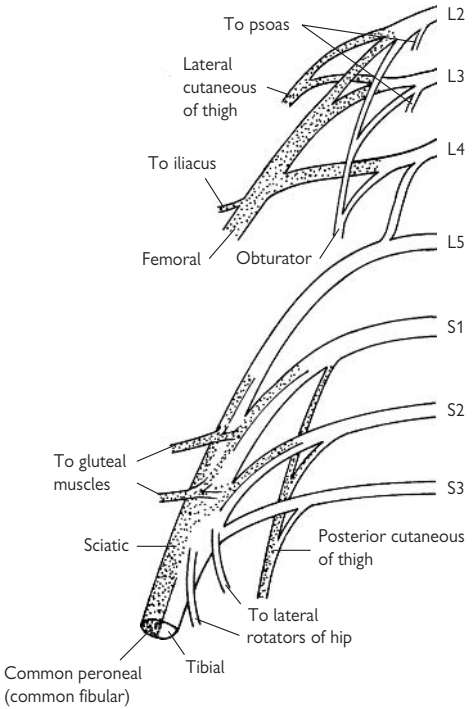

Figure 2.19 Lumbosacral plexus. L2, L3, L4, L5 refer to the second to fifth lumbar roots. S1, S2, S3 refer to the first to third sacral roots. (Reproduced with permission from MacKinnon, P, Morris, J [2005]. *Oxford Textbook of Functional Anatomy*, Vol. 1, 2nd ed., Oxford, England: Oxford University Press.)

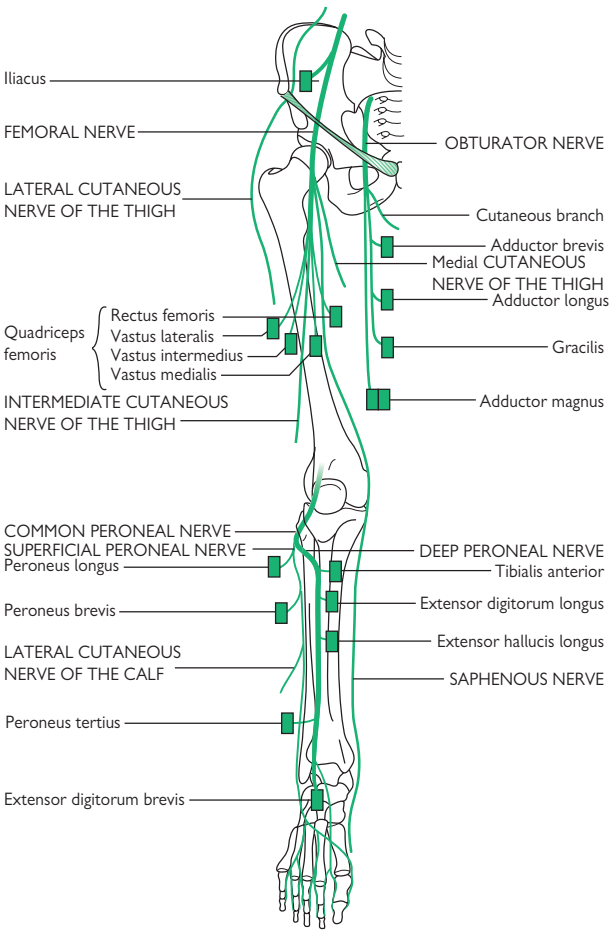

Figure 2.20 The nerves of the anterior aspect of the lower limb, their cutaneous branches, and the muscles that they supply. (From *Aids to the Examination of the Peripheral Nervous System*, 4th ed., W.B. Saunders, On behalf of the guarantors of *Brain*.)

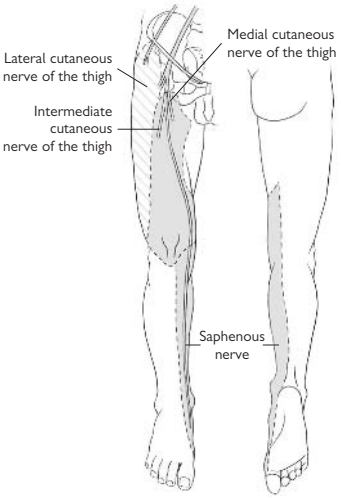
Lateral cutaneous nerve of the thigh
Intermediate cutaneous nerve of the thigh
Medial cutaneous nerve of the thigh
Saphenous nerve

Figure 2.21 Cutaneous distribution of the femoral nerve and lateral femoral cutaneous nerve.

Figure 2.22 Cutaneous distribution of the obturator nerve. L2–L4 refers to the second, third, and fourth lumbar roots.

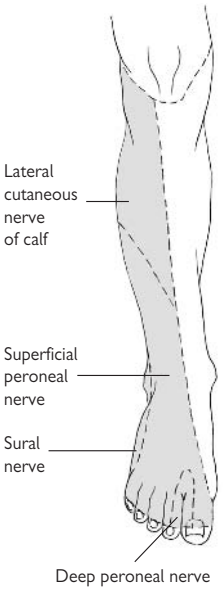

Figure 2.23 Cutaneous distribution of the common peroneal nerve.

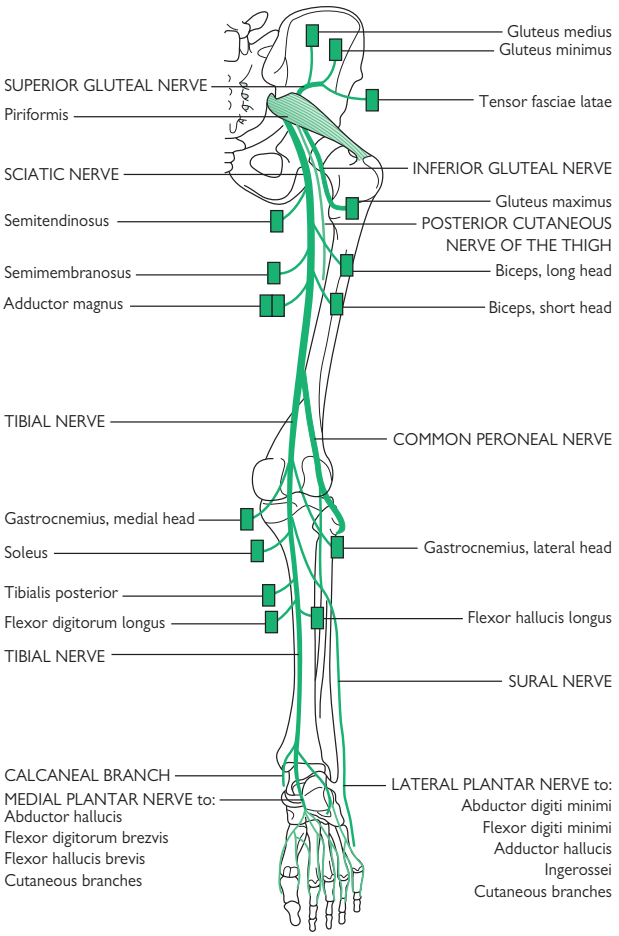

Figure 2.24 The nerves of the posterior aspect of the lower limb, their cutaneous branches, and the muscles that they supply. (From *Aids to the Examination of the Peripheral Nervous System*, 4th ed., W.B. Saunders, On behalf of the guarantors of *Brain*.)

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Chapter 3

Common clinical presentations

Ann A. Little, MD

Delirium *52*
Loss of consciousness *53*
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Acute headache (thunderclap headache) *60*
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Delirium

Delirium is a disturbance of consciousness accompanied by a change in cognition not explained by a preexisting or progressive dementia, developing over a short period of time (hours to a day) and with a fluctuating course. The following features are seen:

- Reduced awareness of the environment (disorientation) associated with difficulties with attention (focusing, maintaining, or shifting)
- Cognitive impairment
  - Memory impairment and language disturbance (e.g., dysnomia, dysgraphia)
  - Perceptual disturbance (e.g., misinterpretation, illusions, hallucinations)
- Fluctuating course with symptoms often worse at night

Associated features include the following:

- Disruption of sleep–wake cycle
- Increased or decreased psychomotor activity
- Emotional disturbances (anxiety, anger, fear, depression, irritability, euphoria, apathy) with rapid shift of state at times

Etiology

- Focal brain disorders
  - Head injury, stroke, increased intracranial pressure, intracranial infection, seizures
- Systemic Illness
  - Infection, cardiovascular compromise, pulmonary compromise, endocrine abnormalities
- Medications/substances
  - Intoxication
  - Withdrawal

Diagnosis

- History and examination
- Complete blood count with differential and platelet count (CBC-PD), electrolytes, kidney and liver function, glucose
- Urine analysis (UA) and culture, blood cultures, skin examination, chest radiograph (CXR)
- Thyroid studies, cardiac enzymes, blood gases
- Human immunodeficiency virus (HIV) and syphilis testing
- Toxicology screen
- Lumbar puncture
- Electroencephalogram (EEG)
- Head computed tomography (CT) or magnetic resonance imaging (MRI)

Management

- Correct metabolic abnormalities
- Treat infection or other underlying medical issues
- Assess medications
- Benzodiazepines for alcohol and substance withdrawal
- Antipsychotics for behavioral control in appropriate cases
- Provide reorientation

- Assess and correct sensory deprivation (glasses, hearing aids)
- Try to restore sleep–wake cycle

Delirium occurs in 10%–20% of hospitalized patients, with highest rates in the frail and elderly. Predisposing factors are age, presence of dementia, and impaired physical or mental health.

Loss of consciousness

This is a common problem.

- Obtaining a history (from patient and/or eyewitness) is essential.
- Cause may remain idiopathic in up to ~40% of patients.
- Advise the patient about implications for driving in accordance with state guidelines. Discuss safety issues (avoidance of climbing, operating dangerous machinery, swimming alone, bathing alone).

Etiology

Neurological causes

- Epileptic seizures—the most common cause
- Raised intracranial pressure (ICP); tumor, especially posterior fossa lesions; hydrocephalus due to, e.g., colloid cyst
- Subarachnoid hemorrhage (SAH)
- Sleep disorders (narcolepsy, cataplexy)
- Basilar artery migraine (rare)
- Cerebrovascular disease (rare, unless massive stroke or brainstem)

Neurally mediated syncope (neurocardiogenic)

- Vasodepressor syncope (hereditary disposition; common in young women; seen with heat, alcohol intake, hunger, pain, strong emotion), the most common cause
- Carotid sinus syncope
- Situational syncope (cough, micturition, valsalva maneuvers)
- Vasovagal events

Cardiac syncope

- Cardiac arrhythmias (reduced cardiac output due to brady- or tachyarrythmias, asystole), the most common cause
- Structural cardiopulmonary disease (aortic stenosis, hypertrophic cardiomyopathy, pulmonary embolus, cardiac tamponade)
- Depleted intravascular volume (hemorrhage, dehydration)

Orthostatic or postural hypotension

- Drugs, the most common cause (e.g., vasodilators, antidepressants, L-dopa preparations)
- Autonomic neuropathy (Guillain–Barre syndrome, diabetes, amyloid)
- Autonomic failure (multiple system atrophy [MSA], PD)
- Addison disease

Metabolic disorders

- Hypoglycemia
- Hyperventilation-induced alkalosis
- Anemia

- Hypoxia

Psychiatric disorders

- Psychogenic nonepileptic attacks (the most common cause).

Diagnosis

See Table 3.1. Key points of history aid in diagnosis.

Investigations

Consider the following:

- Blood: CBC (anemia); glucose (especially in diabetics or if preprandial); basic metabolic panel (electrolytes)
- Serial blood pressure readings supine and standing to detect immediate or delayed orthostatic hypotension
- Electrocardiogram (ECG); Holter monitor; echocardiogram for cardiac syncope
- Tilt table testing: sensitive for syncopal tendencies
- EEG by itself does not diagnose (or rule out) epilepsy. Fifty percent false-negative rate for interictal EEG in patients with epilepsy. Reduced to 30% by repeating and 20% with sleep-deprived EEG. False-positive EEG in up to 2% healthy young adults.
- Ictal video-EEG-telemetry most sensitive and specific test for epilepsy. Note: frontal lobe epileptic seizures may appear normal even on ictal EEG.
- Imaging—Head CT or MRI (preferable)—for focal seizures, focal signs, or signs and symptoms of increased ICP.

Table 3.1 Features differentiating vasovagal syncope from epileptic seizures

	Seizure	Syncope
Trigger	Rare—flashing lights, hyperventilation	Common (blood, needles, hot environment, standing, pain)
Prodrome	Common—auras	Very common—nausea, lightheadedness, tinnitus, graying vision
Onset	Sudden	Gradual
Duration	1–3 min	1–30 sec
Convulsive jerks	Common—prolonged	Common—brief
Incontinence	Common	Uncommon
Tongue biting	Common	Rare
Post-event confusion	Common	Rare
Color	Pale, cyanotic (tonic–clonic seizures)	Very pale

Acute vertigo

Vertigo is the illusion of rotation caused by asymmetry of neural activity between the right and left vestibular nuclei. Bilateral damage does not cause vertigo.

It is essential to determine if the vertigo is central or peripheral because cerebellar infarction/hemorrhage can be life-threatening and require neurosurgical intervention.

Etiology

Mechanical

- Benign paroxysmal positional vertigo (BPPV): loose calcium carbonate crystals (otoliths) moving within a semicircular canal with head movement and change of position (most common cause of acute vertigo).

Infectious

- Acute vestibular neuritis or labyrinthitis, presumed viral, affects lateral semicircular canal function.

Vascular

- Infarction resulting from occlusion of the anterior vestibular artery, a branch of the internal auditory artery from the anterior inferior cerebellar artery (AICA).
- Brainstem stroke, with associated signs (e.g., Horner syndrome, dysarthria, incoordination, diplopia, facial numbness)
- Inferior cerebellar infarction can present with only vertigo, nystagmus, and postural instability.
- Vertebrobasilar ischemia, with associated brainstem signs

Inflammatory

- Multiple sclerosis can produce an evolving vestibular syndrome with a plaque around the 8th nerve root entry zone.

Structural

- Perilymphatic fistula, spontaneous or traumatic

Metabolic

- Meniere syndrome: endolymphatic hydrops
- Drug toxicity

Clinical features

Clinical presentation is with acute-onset vertigo, nausea, and vomiting.

Spontaneous nystagmus

- Peripheral origin is indicated by the following characteristics:
  - Horizontal with a torsional component
  - Does not change direction with a change in gaze
  - Slow phase toward affected ear; fast phase toward unaffected ear
  - Decreased by visual fixation. At bedside, remove fixation and assess nystagmus using Fresnel lenses, blank sheet of paper in front of patient's eyes, or an ophthalmoscope focused on the optic disc with the patient's other eye covered. Nystagmus should be evident in the primary position. Note that the direction of the nystagmus is inverted when viewed through the ophthalmoscope.

- Central origin is indicated by the following characteristics:
  - Often purely horizontal or vertical or torsional
  - Changes in direction with changes in the position of the gaze (i.e., bi- or multidirectional).
  - Visual fixation has little effect on nystagmus of central origin.
- Caveat: horizontal—torsional nystagmus may occur in both peripheral and central disorders.

The head thrust test: a bedside test of the horizontal vestibulo-ocular reflex (see Fig. 3.1).

- Indicates absent lateral semicircular canal function on affected side
- If a catch-up saccade occurs in one direction and not the other, this indicates a peripheral vestibular lesion on that side within the labyrinth or the 8th nerve, including the root entry zone in the brainstem.

Fukuda or Unterberger test Marching in place (60 steps) with eyes closed and arms out. Positive test—patient veers to side of the lesion (>45 degrees). Patients with cerebellar lesion are unable to stand unaided to do test. Does not discriminate between central and peripheral causes.

Other signs

- Patients with a peripheral lesion can typically stand but veer/tilt to the side of the lesion. Those with a central lesion are often unable to stand without support.
- If signs are not typically peripheral, then assume central and investigate.

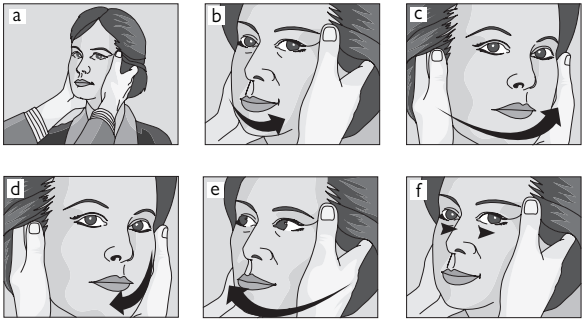

Figure 3.1 The head thrust test. The examiner turns the patient's head as rapidly as possible about 15° to one side and observes the ability of the patient to keep fixating on a distant target. The patient illustrated has a right peripheral lesion with a severe loss of right lateral semicircular canal function. While the examiner turns the patient's head toward the normal left side (top row), the patient is able to keep fixating on target. By contrast, when the examiner turns the patient's head to the right, the vestibulo-ocular reflex fails and the patient cannot keep fixating on target (e) so that she needs to make a voluntary rapid eye movement, that is, a saccade, back to target (f) after the head impulse has finished; this can be easily observed by the examiner. It is essential that the head is turned as rapidly as possible; otherwise smooth pursuit eye movements will compensate for the head turn. (Reproduced with permission from Halmagyi, GM [2005]. Diagnosis and management of vertigo. *Clin Med* **5**(2):159–165. Royal College of Physicians.)

Recurrent attacks of acute vertigo May be due to one of the following:

- BPPV
- Ménière disease
- Migraine
- Posterior circulation transient ischemic attacks (TIAs) (rare); brief crescendo of attacks heralding stroke. Some may be associated with diplopia, dysarthria, or facial numbness.
- Episodic ataxia

Differential diagnosis (see Table 3.2)

Management

- If peripheral, treat with vestibular sedatives such as benzodiazepines (e.g., diazepam 5–10 mg q12hr, or antihistamines, e.g., meclizine 25–50 mg q6hr). Antiemetics and anticholinergice drugs (scopolamine patch) may also be used. Symptoms always resolve in a few days due to vestibular compensatory mechanisms. If BPPV suspected, assess with Dix-Hallpike maneuver (Fig. 3.2) and treat with Epley maneuver (Fig. 3.3) for resolution.

Table 3.2 Differential diagnoses of acute vertigo

Cause	History	Examination	Investigation
Benign paroxysmal positional vertigo	Abrupt onset triggered by positional change	Dix-Hallpike or Barany maneuvers will reproduce symptoms	Epley maneuver: diagnostic and curative
Acute vestibular-neuritis or labyrinthitis	Develops over hours and resolves in days; viral infection	Spontaneous "peripheral" nystagmus, positive head thrust test	Unilateral caloric hypoexcitability, audiogram normal. MRI normal
Labyrinthine infarction	Abrupt onset; previous vascular disease	As for vestibular neuritis	As for neuritis; MRI-silent infarcts
Perilymph fistula	Abrupt onset; associated head trauma, barotrauma, coughing or sneezing; may be associated with chronic otitis and cholesteatoma	As for neuritis; possible perforation of tympanic membrane. Positive fistula test (vertigo and nystagmus induced by pressure in the external canal)	As for labyrinthitis; CT temporal bone may show erosion from cholesteatoma
Brainstem and cerebellar infarction	Abrupt onset; history of vascular disease; other neurological symptoms	Spontaneous central nystagmus; head thrust test positive only if root entry zone involved; focal neurological signs	Unilateral caloric hypoexcitability if anterior inferior cerebellar artery involved. MRI shows infarction in medulla, pons, or cerebellum.

Note: Ménière syndrome can initially present with acute vertigo, but it rarely lasts more than 24 to 36 hours (other symptoms: low frequency tinnitus, hearing loss, and a sense of fullness in the ears).

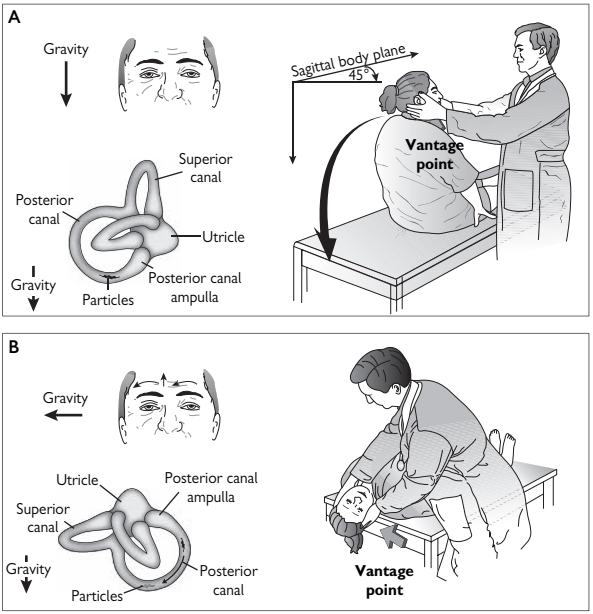

Figure 3.2 Dix Hallpike maneuver in diagnosis of BPPV. (From Furman JM, Cass SP [1999]. Benign paroxysmal positional vertigo. *New Engl J Med* **341**:1590–1596. Copyright ©1999 Massachusetts Medical Society. All rights reserved.)

- If central, consider CT to exclude a cerebellar infarction or hemorrhage. MRI is more sensitive for detection of posterior fossa infarcts. Infarction with cerebral edema may result in hydrocephalus, requiring urgent shunting and/or decompression.
- Many posterior circulation infarcts are due to cardiogenic embolism.
  - ECG, 24-hour ECG, transthoracic and/or trans-esophageal echo

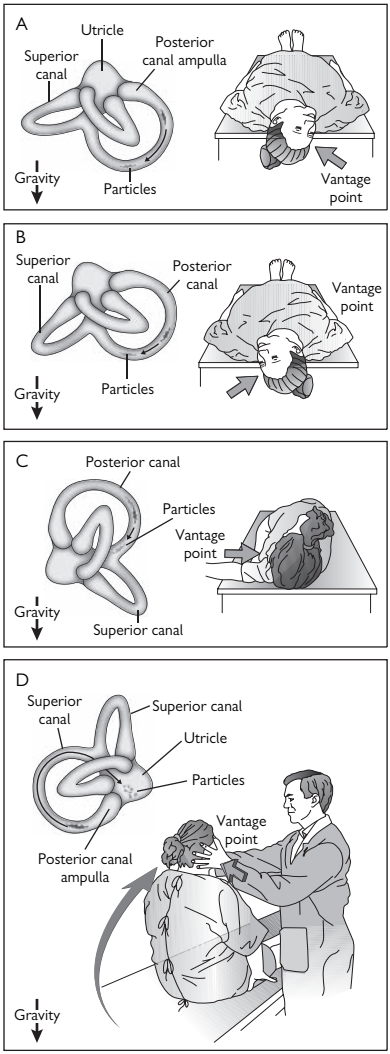

Figure 3.3 Epley maneuver as treatment for BPPV. (From Furman JM, Cass SP [1999]. Benign paroxysmal positional vertigo. *New Engl J Med* **341**:1590–1596. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

Acute headache (thunderclap headache)

- Two percent of visits to the emergency department (ED) are due to headache.
- In patients with "worst-ever" headache and a normal neurological examination, 12% may have a subarachnoid hemorrhage (SAH). If neurological examination is abnormal, this becomes 25%. The diagnosis of SAH is missed initially in up to 32% of cases.

"Thunderclap headache" may be defined as an abrupt onset, often a "worst-ever" headache that is maximal in seconds but may develop in minutes.

Differential diagnoses

Vascular causes

- SAH
- Carotid and vertebral artery dissection
- Cerebral venous thrombosis
- Arterial hypertension
- Temporal arteritis

Nonvascular causes

- Meningoencephalitis
- Intermittent hydrocephalus (colloid cyst of the 3rd ventricle)
- Spontaneous intracranial hypotension

Primary headache syndromes

- Coital cephalgia (headache associated with sexual activity)
- Crash migraine
- Benign cough and exertional headache
- Icepick or idiopathic stabbing headache
- Exploding head syndrome

Clinical features

The "red flags" in a patient with acute headache include the following:

- "Worst-ever" headache
- Onset with exertion (20% of SAH occur with exertion, e.g., sexual intercourse)
- Impaired alertness or conscious level, neck stiffness, progressive neurological deterioration
- Abnormal neurological examination (3rd or 6th nerve palsy), papilledema, subhyaloid hemorrhage, hemiparesis, or diplegia (anterior communicating aneurysm)
- Loss of visual acuity or visual fields; tenderness to palpation of temporal arteries

Investigations

All patients should have a CT scan to assess for hemorrhage, focal mass effect, or signs of increased intracranial pressure.

Five percent of CT scans in patients with SAH are normal initially. Sensitivity to detect blood decreases with time, from 95% on day 1, 50% on day 7, 30% on day 14, to almost 0% on day 21.

If the CT scan is negative, an LP should be performed providing there are no contraindications (e.g., signs of increased ICP).

- Always measure opening pressure—elevated in (60% of) SAH, in cerebral venous thrombosis, and in meningitis.
- Sample should be centrifuged immediately and the CSF compared to plain water in a glass tube against a white background. Although spectrophotometry is more sensitive than visual inspection in looking for xanthochromia, it is not widely available.
- In SAH, usually >100,000 RBC + 1–3 WBC per 1000 RBC. If there are a lot more white cells, consider meningitis complicated by a traumatic tap. (See Table 3.3.) Alternatively, after a few days following a SAH, a meningitic reaction may occur.
- Xanthochromia, resulting from breakdown of hemoglobin to oxyhemoglobin (pink) and bilirubin (yellow), may take at least 12 hours to develop; hence the recommendations to delay LP until 12 hours after ictus unless meningitis is a strong possibility. This may disappear after 14 days. (See Table 3.4.)
- Other causes of xanthochromia: jaundice, elevated CSF protein (>1.5 g/L), malignant melanoma, and rifampicin. If CT is positive or there is persistently bloody CSF or xanthochromia by visual inspection, cerebral angiography and a neurosurgical opinion are necessary.

Table 3.3 CSF: SAH versus traumatic tap

	SAH	Traumatic tap
Opening pressure	Increased	Normal
Xanthochromia	Yes	No
Clearing of RBCs (tube 1→4)	No	Yes

Table 3.4 Rule of "halves": CSF findings in SAH*

1/2 hour	RBC appear
1/2 day	Xanthochromia appears
1/2 week	RBCs disappear
1/2 month	Xanthochromia disappears

*Rough estimates.

Acute neuromuscular weakness

Acute flaccid paralysis may be due to disorders of:

- Nerve
- Muscle
- Neuromuscular junction

In the early stages of an acute myelopathy due to trauma or an intraspinal hemorrhage or myelitis due to inflammatory or infectious causes, clinical signs may resemble those of a peripheral rather than a central disorder.

Clinical features

- The tempo of progression will give a clue to etiology—sudden-onset paraparesis, e.g., is most likely to be due to a vascular insult to the spinal cord such as anterior spinal artery (ASA) thrombosis.
- Most of the neuromuscular causes tend to have a subacute course progressing over a few days.
- Exceptions are the periodic paralyses (both hyperkalemic and hypokalemic). Key finding is depressed or absent reflexes, which will also be found in weakness due to secondary hypokalemia. In the periodic paralyses, attacks may last minutes or hours in hyperK-PP and hours/days in hypoK-PP.
- Significant sensory deficit is unusual in Guillain–Barre syndrome (GBS), whereas a pure motor deficit without sensory loss is unusual in vasculitic neuropathy.
- A sensory level and sphincter dysfunction implies a spinal cord disorder. Spinal cord compression without pain and a sensory level are unusual.
- Back pain (severe) may be a feature of GBS.
- Autonomic dysfunction occurs in GBS, but pupillary dilatation and hypersalivation are found in botulism. Persistent hypertension and tachycardia in association with pure motor weakness occurs in porphyria.

Differential diagnosis See Table 3.5.

Table 3.5 Differential diagnosis of acute neuromuscular weakness

Disorder	Clinical features	Investigations
Peripheral nerve disorders		
Guillain–Barré syndrome	Subacute onset but may be sudden, few sensory signs; no sphincter involvement. Vascular autonomic dysfunction; no sensory level	NCS show slowing but may be normal; CSF protein increased, few cells 10–20.

Table 3.5 (*Contd.*)

Disorder	Clinical features	Investigations
Vasculitic neuropathy	Patchy motor and sensory loss; pain and dysesthesia. Underlying primary vasculitic or rheumatological syndrome	NCS may reveal clinically asymptomatic lesions. Nerve ± muscle biopsy
Acute intermittent porphyria	Distal motor neuropathy, hypertension, and tachycardia	Blood and urine analysis
Diphtheria	Oropharyngeal weakness at onset; pharyngeal membrane	NCS—axonal neuropathy; serology
Heavy metal poisoning, e.g., lead, arsenic	Motor neuropathy, abdominal pain, blue gum line (lead), Mees lines (arsenic)	Serum lead level, serum arsenic, urine or serum heavy metal screen
Neuromuscular junction disorders		
Myasthenia gravis	Fluctuating muscle weakness, ocular, bulbar, respiratory involvement. Reflexes intact	Tensilon test, ACh receptor antibodies. EMG studies show decrement. Single fiber—jitter and blocking
Lambert–Eaton syndrome	Variable muscle weakness. Ocular, muscles spared. Underlying carcinoma	Voltage-gated calcium channel antibodies. Motor NCS show facilitation (usually >200%) with 15 sec exercise.
Botulism	Muscle weakness, ophthalmoplegia with pupillary and autonomic changes	Isolation of organism from wound; serology
Muscle disorders		
Inflammatory myopathy	Muscle pain and weakness, usually proximal. Rhabdomyolysis	CPK increased, EMG myopathic; muscle biopsy
Hypokalemic periodic paralysis	Autosomal dominant. Duration: hours to days. Triggers: rest after exercise, carbohydrate meal, stress	Short exercise NCS, mutation in *CACNA1S* gene (calcium channel)

Table 3.5 (*Contd.*)

Disorder	Clinical features	Investigations
Hyperkalemic periodic paralysis	Autosomal dominant. Duration: minutes to hours. Triggers: rest after exercise, K^+-containing foods	Short exercise NCS, mutation in *SCN4A* gene (sodium channel)
Anterior horn cell disorder		
Due to poliovirus or other enteroviruses	Acute lower motor neuron syndrome	Stool culture; CSF PCR
Myelopathic disorders		
Acute transverse myelitis	Initially flaccid rather than spastic. Sphincter involvement, sensory level. May be first episode of demyelination or viral, e.g., Herpes varicella zoster	MRI spine ± brain; CSF for oligoclonal bands; PCR
Anterior spinal artery syndrome	Acute flaccid paralysis with sensory level. Sparing of posterior columns	MRI thoracic spine cardiac, thrombophilia, vasculitic screen
Functional disorders	Bizarre gait, Hoover sign, nonorganic sensory level	MRI and CSF to xclude organic disorder

Acute focal neurological syndromes

In patients who present with acute focal neurological deficit, the history and examination should point to the site of pathology and to the possible pathological mechanism(s).

Etiology of acute focal neurological symptoms and signs

- TIA/stroke
- Migraine aura
- Partial (focal) seizure
- Intracranial structural lesions
  - Tumor (hemorrhage or blockage of CSF flow)
- Vascular rupture
  - Subdural or epidural hematoma, arteriovenous malformation (AVM), aneurysm
- Multiple sclerosis and inflammatory central nervous system (CNS) disorders
- Metabolic disorders

  - Hypoglycemia
  - Hypo- and hypercalcemia
  - Wernicke encephalopathy
- Meningoencephalitis
  - Cerebral abscess
  - Associated vasculitis
  - Specific organisms, e.g., herpes simplex and temporal lobes, *Listeria monocytogenes* and brainstem involvement
- Other disorders
  - Myasthenia gravis
  - Hyperventilation and panic attacks
  - Somatization disorders

Clinical notes

Onset of symptoms

- Sudden onset of focal neurological dysfunction without warning suggests a vascular etiology.
- Slow progression ("march") of symptoms over a few seconds suggests an ictal phenomenon.
- Progression over minutes or hours points to a migrainous diathesis.
- Exceptions to these rules occur since occasionally a stroke may progress in a stepwise manner over hours or days.
- Gradual development of focal neurological deficit over days or weeks and months indicates a space-occupying lesion such as tumor.

Duration of symptoms *Only factor that distinguishes a TIA from a stroke is the duration of TIA is <24 hours although most episodes last only a few minutes. MRI imaging may or may not reveal infarction.*

Nature of symptoms

- Cerebrovascular events cause negative symptoms and signs, i.e., loss of sensory, motor, language, or visual function.
- Ictal events generally cause positive phenomena such as tingling in an arm or leg.
- Migraine may cause both positive and negative symptoms and signs—tingling marching up the arm and dysphasia.
- Space-occupying lesions will result in a progressive loss of function or may trigger positive ictal symptoms.

Additional symptoms and signs

- Associated throbbing unilateral headache during or after the development of neurological symptoms point to migraine, but headache occurs in 15% of patients with TIAs, 25% of patients with acute ischemic stroke, and all cases of subarachnoid hemorrhage.
- Carotid and vertebral artery dissection may cause focal neurological deficits in association with head, face, neck, or ocular pain.
- In an elderly patient with monocular visual loss, temporal arteritis needs exclusion.
- Subdural hematoma may present with an acute onset with or without headache.

- Partial seizures may progress rapidly to generalized tonic clonic seizures.
- Two percent of patients presenting with an acute stroke may have a seizure, either partial or generalized, at onset.
- Meningoencephalitis may present with symptoms and signs such as headache, neck stiffness, and photophobia as well as focal signs due to an associated vasculitis.

Loss of consciousness

- TIA and ischemic stroke patients very rarely present with loss of consciousness.
- If it does occur, the most likely causes are SAH, a large brain stem stroke, or a massive hemispheric intracerebral hemorrhage.
- Large hemispheric ischemic strokes may progress to coma after a few days (due to swelling and/or secondary hemorrhage).
- Following a seizure, some patients may present with a Todd paresis.

Spastic paraparesis

Bilateral upper motor neuron signs in the legs. A common presentation caused by a variety of disorders (hereditary and acquired).

Etiology

See Table 3.6. In cases of undiagnosed spastic paraparesis, consider a trial of L-dopa for dopa-responsive dystonia.

Clinical features

- Gait is effortful and stiff at knees and hips: "walking through mud." Observe gait for fixed mild flexion at knees and hips, "scissoring" of legs, circumduction, short steps, lateral movement of trunk while ambulating.
- Tendon reflexes are hyperactive.
- Check for a sensory level—anterior and posterior.
- In degenerative conditions the abdominal reflexes remain, e.g., motor neuron disease.
- Patients presenting with a short history, associated back pain, and bladder and bowel symptoms (urgency, incontinence)—emergency assessment necessary (for cord compression).
- Lesions at lower end of spinal cord above L1 and involving cauda equina, e.g., dural AVM, will have a mixture of upper and lower motor neuron signs, e.g., extensor plantars and absent ankle jerks.
- Hereditary spastic paraparesis may be pure (spastic paraparesis only) or associated in a syndromic fashion with other findings (e.g., deafness, epilepsy, muscular atrophy, ataxia, and dementia).
- Onset early (infancy or childhood) or late (adulthood throughout the life cycle)

Table 3.6 Causes of spastic paraparesis

Cause	Comment
Structural causes	
Parasagittal lesion	E.g., meningioma or dominant anterior cerebral artery infarction affecting medial areas of both frontal lobes
Spinal disease	Cervical or thoracic disc disease
Degenerative disease Syringomyelia Tumors	Typically affecting spinothalamic fibers with sparing of posterior column fibers; anterior horn cell damage causes wasting of hand muscles if syrinx in cervical/thoracic region Intradural and extradural, e.g.,meningioma
Inflammatory/autoimmune disorders	
Demyelination, e.g., MS	Investigations: MRI brain, cord, oligoclonal bands in CSF, VEPs
Sarcoidosis	Investigations: MRI with gadolinium; blood and CSF ACE; CXR, gallium, or PET scan; histology, e.g., skin, liver, muscle
Vascular disorders	
Anterior spinal artery syndrome	Level T10 (artery of Adamkiewicz), sparing posterior column
Spinal AVM	Investigations: MRI/A
Hereditary disorders	
Adrenoleukodystrophy Hereditary spastic paraparesis	Investigations: VLCFA; MRI; ACTH stimulation tests Diagnosis: family history; genetic testing
Infections	
HIV vacuolar myelopathy	Investigations: HIV test; CD4; viral load
Syphilis	Investigations: blood and CSF VDRL,TPHA
HTLV –1	Investigations: blood and CSF HTLV-1
Metabolic disorders	
B_{12} deficiency	Investigations: B_{12},methylmalonic acid
Copper deficiency	Investigations: serum copper, zinc levels
Lathyrism, cassavaism	Dietary history
Cerebral palsy (spastic diplegia)	Birth history; nonprogressive
Degenerative disorders	
Motor neuron disease (primary lateral sclerosis)	Investigations: MRI brain, cord; EMG/ CSF

Ataxia

Ataxia implies incoordination and results from disorders of:
- Cerebellum and its associated pathways
- Loss of proprioceptive sensory input in peripheral nerve disorders and in spinal cord lesions affecting the posterior columns (sensory ataxia)

Cerebellar disease

Signs of cerebellar disease
- Gait ataxia—wide based, reeling. May be more apparent when turning or stopping suddenly. When mild, only tandem gait may be impaired.
- Dysmetria—an inability to perform finger-to-nose movements accurately with overshoot or undershoot and a similar inability on heel/shin testing
- Dysdiadokinesia—inability to perform rapid alternating movements
- Tremor—intention or "hunting" tremor (kinetic) arising from proximal joints (shoulder, hip). Postural (static) tremors may also occur.
- Loss of rhythm—tested by rapid tapping on the back of the hand or tapping the heel on the opposite knee
- Hypotonia
- Dysarthria—with ataxic dysarthria as words are broken up into syllables; impaired modulation of volume
- Eye movements—broken-up pursuit movements; overshooting or undershooting targets with saccadic eye movements (saccadic dysmetria). Macrosaccadic square wave jerks in primary position (sudden short duration movements laterally with rapid correction—may need to view optic disks to appreciate)
- Nystagmus—coarse nystagmus with the fast phase in the direction of the lesion; multidirectional nystagmus
- Hyporeflexia

Differential diagnoses of acquired cerebellar ataxia
- Toxic: alcohol
- Drugs:
  - Phenytoin
  - Lithium
- Vascular:
  - Ischemic stroke
  - Hemorrhage
- Inflammatory: demyelination (MS, ADEM)
- Neoplastic:
  - Metastases (breast, bronchus)
  - Primary brain tumors (in children, pilocytic astrocytoma and medulloblastoma)
  - Paraneoplastic syndrome, associated with small-cell lung cancer (anti Hu, anti PCA2, ANNA 3); ovarian cancer (anti Yo), breast cancer (anti Yo and Ri), and testicular cancer (anti Ta/Ma2); Hodgkin lymphoma (anti Tr); neuroblastoma (anti Hu); and thymoma (anti CRMP5/CV2)

- Infectious/post infectious:
  - Viral cerebellitis (measles)
  - SSPE
  - HIV
  - Miller Fisher syndrome (ataxia, areflexia, ophthalmoplegia + GQ1b antibody)
- Prion: sporadic or variant *Creutzfeldt-Jakob disease* (CJD)
- Structural:
  - Arnold–Chiari malformation
  - AVM
  - Basilar invagination (Paget disease)
- Degenerative: cerebellar variant of MSA
- Nutritional or GI related:
  - Vitamin E deficiency;
  - Thiamine (B_1 deficiency) in, e.g., Wernicke encephalopathy
  - Celiac disease (with myoclonus)
- Endocrine: decreased T4

Differential diagnoses of hereditary cerebellar ataxias

- In general the autosomal dominant ataxias (ADCAs) and the other autosomal disorders that may have ataxia as an additional feature such as HD, dentatorubral pallidoluysian atrophy (DRPLA), Gerstmann–Straussler–Scheinker (GSS) tend to present >25 years of age.
- Autosomal recessive ataxias, inborn errors of metabolism, mitochondrial disorders, and episodic ataxias present <25 years of age.

Autosomal dominant cerebellar ataxias (ADCA)

- There are at least 30 spinocerebellar ataxia genes. Ataxia in combination with any of the following—pyramidal, peripheral nerve, ophthalmoplegia, dementia. Absence of a family history does not exclude the possibility of diagnosis.
  - SCA 2—slow saccades, upper limb areflexia
  - SCA 3—dystonia, parkinsonism, facial myokymia, bulging eyes
  - SCA 6—"pure cerebellar syndrome"
  - SCA 7—pigmentary macular dystrophy

Recessive ataxias—See Table 3.7.

Inborn errors of metabolism

- Hexoaminidase A or B deficiency
- Adrenoleukodystrophy
- Wilson disease

Episodic ataxias—See Table 3.7.

Mitochondrial disorders with ataxia

- NARP (neuropathy, ataxia, retinitis pigmentosa)
- MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes)
- MERRF (myoclonic epilepsy with ragged red fibers)

Table 3.7 Differential diagnoses of autosomal recessive cerebellar ataxias

Disease	Age of onset yrs (range)	Clinical/laboratory features	Genetics
Friedreich ataxia	5–15 (0–60)	Kyphoscoliosis, pes cavus, lower limb areflexia, extensor plantars, axonal neuropathy, cardiomyopathy, impaired glucose tolerance test	Frataxin gene, chr 9q13
Ataxia telangectasia	1–6 (0–20)	Decreased IgG and IgA (increased infections), skin and conjunctival telangectasia, oculomotor apraxia, chorea, dystonia, hypogonadism, absent lower limb reflexes	ATM, chr 11q22.3
Ataxia with oculomotor apraxia type 1	2–6 (2–18)	Common in Japan, Portugal. Oculomotor apraxia, chorea, cognitive impairment, areflexia, severe axonal neuropathy. Decreased albumin, increased cholesterol, increased LDL, decreased HDL	Aprataxin, chr 9p13.3
Abetalipoproteinemia	2–17	Friedreich phenotype + steatorrhea, retinitis pigmentosa, distal amyotrophy, acanthocytes, absent VLDL/LDL, decreased cholesterol, decreased vitamin A, E, K	Microsomal triglyceride transfer protein (MTP), chr 4q22
Ataxia with vitamin E deficiency	2–20 (2–52)	Friedreich phenotype + head titubation. No cardiomyopathy or decreased GTT. Vitamin E decreased	Alpha tocopherol protein, chr 8q13.

Sensory ataxia

Clinical features

Any marked loss of proprioception will result in sensory ataxia.

- Signs of a neuropathy with loss of joint position sense
- Pseudoathetosis of fingers when arms outstretched and eyes closed
- Upper limb position sense loss is tested by attempting to bring both horizontally outstretched index fingers together in the midline with eyes closed.
- Heel-shin testing deteriorates with eye closure.
- Positive Romberg sign

Differential diagnoses of sensory ataxia

- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Paraproteinemic neuropathy (IgM)

- Refsum disease (due to defect in phytanic acid metabolism. Other features include deafness, retinitis pigmentosa). A rarer defect of pristanate metabolism presents in a similar fashion (Massion Vernier disease).
- Sensory ganglionitis (paraneoplastic, Sjögren syndrome, idiopathic)
- Friedreich ataxia has a significant peripheral nerve component.
- Spinal cord disorders (affecting posterior columns):
  - Cervical spondylosis
  - Demyelination (MS)

Acute visual failure (Table 3.8)

Monocular transient visual loss

- Amaurosis fugax due to emboli from carotid vessels or heart.
  - Sudden onset lasting 5–15 minutes. Described as a curtain being pulled downwards in front of the eye. Loss may be quadrantic or total and may be accompanied by contralateral limb signs due to ipsilateral hemispheric ischemia.
- Closed angle glaucoma—accompanied by halos around lights and may not always be associated with redness and pain.
- Transient visual obscurations (TVOs) are a gray-out precipitated by postural change or straining. Causes:
  - Chronic papilledema due to increased ICP
  - Hypotension and hypoperfusion
  - TVOs that are gaze-evoked suggest orbital tumors.
- Retinal migraine is rare and results from transient vasospasm that responds to calcium channel blockers.

Bilateral, transient visual loss

- Usually due to transient visual cortical dysfunction.
- In patients under the age of 40 years this is most commonly due to migraine.
- Other causes include thromboembolism, hypotension, or hyperviscosity.
- In children may occur post-trauma or as part of the benign occipital epilepsy syndrome in childhood.

Nonprogressive unilateral sudden visual loss

- Usually due to ischemia of the optic nerve or retina
- Anterior ischemic optic neuropathy (AION) presents with infarction of the optic disc and is due to atherosclerosis or temporal arteritis.
- Optic nerve infarction due to embolism is rare.
- Retrobulbar optic nerve infarction (or posterior ischemic optic neuropathy) occurs in the setting of cerebral hypoperfusion perioperatively.
- Central retinal artery or branch occlusion is due to emboli or arteriosclerosis. Field defects may be altitudinal, quadrantic, or total. A cherry red spot at the macula is pathognomonic.

Table 3.8 Differential diagnosis of acute optic neuritis

Diagnosis	Clinical features	Investigations
Corticosteroid responsive optic neuropathy		
Sarcoidosis SLE Autoimmune optic neuropathy Behçet disease Neuromyelitis optica	Progressive severe visual loss, often bilateral, isolated, or part of a multisystem disorder. More common in Africans and Afro-Caribbeans. Relapse on steroid withdrawal.	Gadolinium-enhanced MRI brain and orbits, CSF, ANA, ACE, CXR, Gallium scan, tissue biopsy
Other inflammatory causes		
Post infectious Postvaccinial ADEM Neuro-retinitis	Bilateral, childhood, good prognosis, swollen disc, macular star, spontaneous recovery	*Bartonella, Borrelia,* syphilis serology
Compressive optic neuropathy		
Tumors e.g., meningioma, glioma, pituitary adenoma	Painless, optic atrophy at presentation	MRI, biopsy
Metastases	Painful	
Thyroid ophthalmopathy	Painful	
Aneurysms		
Sinus mucoceles		
Infectious optic neuropathy		
Syphilis TB Lyme disease Viral optic neuritis	Progressive visual loss, disc edema, vitreous cellular reaction	Serology, CSF, CXR, tuberculin test
Toxic and nutritional optic neuropathy		
Vitamin B_{12} deficiency	Bilateral, symmetrical	B_{12}, homocystine
Tobacco-alcohol amblyopia	Poor prognosis	
Methanol intoxication		
Ethambutol		
Cuban and Tanzanian epidemic optic myelopathy		?dietary

- Central retinal vein occlusion occurs in hypertensives, diabetics, or those with a thrombophilia. A hemorrhagic retinopathy results in a dense central scotoma with preserved peripheral vision.
- Idiopathic central serous chorioretinopathy results from leakage of fluid into the subretinal space. Symptoms include a positive scotoma (black or gray spot in the visual field), metamorphopsia (distortion of images), or micropsia. Fluorescein angiography is necessary for diagnosis.
- Retinal and vitreous hemorrhage

Nonprogressive bilateral sudden visual loss

- Usually a result of an infarct in the visual radiation causing a homonymous hemianopia
- Bilateral occipital infarcts can result in tubular or checkerboard visual fields or total cortical blindness.
- Anton syndrome due to bilateral parieto-occipital infarcts causes cortical blindness accompanied by denial and confabulation.
- Leber hereditary optic neuropathy
  - Maternally transmitted mitochondrial disorder
  - Mutations have been identified at positions 11778, 3460, 15257, and 14484.
  - Presentation is in young men with a rapid permanent loss of central vision.
  - In the acute phase, typical findings include circumpapillary telangiectatic microangiopathy, pseudopapilledema, an absence of fluorescein leakage, and marked arteriolar narrowing.

Visual loss of sudden onset with progression (unilateral)

Usually due to acute optic neuritis. Most common cause is demyelination.

Typical symptoms

- Periocular pain and pain on eye movement
- Progressive visual loss over a few days
- Phosphenes or photopsias (spontaneous flashes of light) on movement
- Spontaneous improvement in vision
- Uhthoff phenomenon—temporary decrease in visual acuity (VA) with increased body temperature after a bath or exercise
- Fading of vision and Pulfrich phenomenon (misperception of the trajectory of moving objects)

Typical signs

- Decreased VA, color vision, and contrast sensitivity
- Variety of field defects including centrocecal scotoma
- Relative afferent pupillary defect (RAPD)
- Optic disc may be normal or swollen.
- Associated uveitis or retinal perivenous sheathing

Coma

Coma is the state of unarousable unconsciousness. The Glasgow Coma Scale (GCS)—see Appendix, p.442—defines coma as:

- Failure to open eyes in response to verbal command (E2)
- Motor response no better than weak flexion (M4)
- Incomprehensible sounds in response to pain (V2)

Neuroanatomy and neuropathology

Consciousness, which is the state of awareness of self and environment with the ability to respond appropriately to stimuli, results from:

- Arousal (ascending reticular activating system)
- Awareness (cerebral cortex)

Coma results from damage to the RAS in the brainstem or extensive bilateral cortical damage.

Etiology

- Head injury
- Medical causes of coma:
  - Cerebrovascular disease (50%)
  - Hypoxic–ischemic injury (20%)
  - Metabolic and infective (30%)

General assessment of coma

History Crucial to contact family, EMS personnel. Obtain PMH, travel, drug details.

General examination

- Temperature (increased or decreased)
- Pulse and blood pressure (septicemia, Addison's disease)
- Skin lesions (rash, needle marks, bruises, pigmentation)
- Respiration:
  - Slow shallow breaths: drug intoxication
  - Deep rapid respiration: metabolic acidosis
  - Periodic respiration: cardiac failure, brainstem lesion
  - Rapid shallow respiration: brainstem lesion
- Breath odor (alcohol, ketones, hepatic, or renal failure)
- Abdominal examination (hepatosplenomegaly in liver or lymphoproliferative disease, polycystic kidneys)
- Otoscopy (blood)

Neurological assessment

- Check for meningismus (meningitis, SAH).
- Fundoscopy:
  - Papilledema
  - Subhyaloid hemorrhages (SAH)
  - Retinopathy (diabetes, hypertension, infection, e.g., choroidal tubercle, HIV)
  - Level of consciousness (GCS). Note if facial injuries or tracheostomy, verbal response unassessable.

Neurological examination: motor and sensory system

Look for asymmetry, evidence of significant cortical (decorticate) or brainstem (decerebrate) damage.

- Observe for seizure activity (focal or general: implies cortical damage)
- Tone
- Posture
- Reflexes, plantar responses
- Response to pain:
  - Using a pen, press nail bed of finger and toe.
  - Apply supraorbital pressure in case of damage to spinothalamic damage in limbs. Flexor response = cortical or upper brainstem injury; extensor response = brainstem injury.

Neurological examination: brainstem function

- Pupillary responses
  - Unilateral fixed dilated pupil (3rd nerve palsy due to tentorial herniation or posterior communicating artery aneurysm)
  - Bilateral fixed dilated pupils: severe brainstem damage or atropine-like drugs used in resuscitation
  - Midpoint, fixed = midbrain lesion
  - Small pinpoint = pontine lesion (also opiates)
  - Small, reactive pupils = diencephalic (thalamus) lesion
  - Horner syndrome = hypothalamus, brainstem, or internal carotid artery lesion
- Eye deviation
  - Conjugate lateral deviation caused by ipsilateral frontal lesion or contralateral brainstem (PPRF) lesion
  - Dysconjugate eyes due to III, IV, or VI palsy or brainstem lesion
  - Skew deviation in brainstem and thalamic lesions
- Spontaneous eye movements.
  - Repetitive horizontal deviations (ping pong gaze) = brainstem lesion
  - Retractory nystagmus (eyes jerk back into orbits) = midbrain lesion
  - Downward ocular bobbing = pontine lesion
- Reflex eye movements (see Fig. 3.4).
  - Oculocephalic maneuver. Head moved side to side—normally eyes deviate to opposite side. If brainstem is affected, eyes remain fixed.
  - Oculovestibular test. First check that tympanic membrane intact. Instill 50–200 mL ice cold water into external auditory meatus: normal tonic response = eyes deviate to side of instillation with nystagmus and quick phase away from side of instillation. Dysconjugate or absent response = brainstem lesion on side of abnormal response.
- Corneal reflex

Classification of coma

Coma without focal signs or meningismus

- Hypoxic–ischemic injury
- Metabolic
- Toxic
- Postictal

Coma with meningismus

- Meningoencephalitis
- SAH

Coma with focal signs

- Hemorrhage
- Infarction
- Abscess
- Tumor
- Hypoglycemia can cause focal signs.

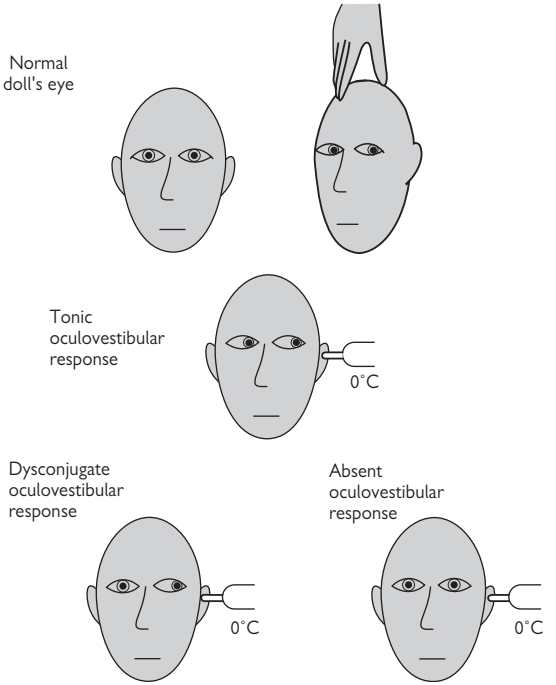

Figure 3.4 Reflex eye movements. (Reprinted from Bates, D [2004]. Coma and brain stem death. *Medicine* **32(**10):69–74. Copyright 2004, with permission from Elsevier.)

Investigations

- Metabolic screen
- CT scan or MRI if possible especially in coma with meningismus or focal signs
- A normal CT does not exclude increased ICP
- EEG (see "EEG and diffuse cerebral dysfunction," p. 396)
- If no contraindications, consider lumbar puncture.

Coma prognosis

Neurologists are often asked to prognosticate on comatose patients in ICU so that decisions about further active treatment can be made. The prognosis can be affected by etiology, as well as depth and duration of coma.

Etiology

- Drug overdose patients have a good prognosis despite significant impairment of brainstem function.
- Likelihood of good recovery:
  - Metabolic or infection, 25%
  - Hypoxic–ischemic injury, 10%
  - Cerebrovascular disease or SAH, 5%

Depth of coma

Within 6 hours:

- If eye opening, 20% chance of good recovery compared to 10% if no eye opening
- No motor response, 3% ; if flexion or better, 15%
- No noise, 8%; groaning, 30%

Duration of coma

The chance of making a good recovery decreases with time.

- By day 3, 7% will make a moderate or good recovery.
- After day 14, 2% will make a moderate or good recovery.
- Patients who remain in coma for >7–15 days will either die or remain in a vegetative state.

Prognostic signs

The data for prognostic signs in coma are poor. No one clinical sign can act as a predictor.

- At 24 hours, if absence of both oculovestibular and corneal reflexes and extension to pain, in the absence of sedative drugs, then chance of a good recovery is <3%.
- Intact pupillary and corneal responses and localization to pain at 24 hours indicates a 40% chance of good recovery.

Brain death

Brain death represents the irreversible cessation of all functions of the brain and brainstem. The determination of brain death is made by a physician based on accepted medical standards. The precise clinical criteria to declare brain death may vary slightly among medical institutions.

General considerations

It is important to identify the conditions leading to brain death. In the absence of etiology, it is difficult to be certain of irreversibility of function. Brain death should not be declared if there is a possibility of intoxication, hypothermia, neuromuscular blockade, cardiovascular shock, or other potentially reversible condition. Any suspected or known reversible condition must be treated and resolved prior to examination for purposes of determining brain death.

Loss of *all* functions of the brain and brainstem must be carefully documented.

Examination

- Absent cerebral function: the patient must be in deep coma and be unresponsive to external stimuli
- Absent brainstem function: the following reflexes must be tested and found to be absent:
  - Pupillary light response
  - Corneal reflex
  - Oculocephalic reflex
  - Oculovestibular reflex
  - Gag reflex
  - Respiratory response to hypercarbia (Box 3.1)

Optional confirmatory tests

- Radionuclide cerebral angiogram to document absence of blood flow to brain and brainstem
- Four-vessel cerebral angiogram to document absence of blood flow to brain and brainstem
- EEG to verify irreversible loss of cerebral cortical function EEG for the purpose of documenting brain death must be performed according to strict criteria of the American Electroencephalographic Society.

In general, most institutions require at least two examinations performed by a physician (often a neurologist or neurosurgeon) not directly involved in the care of the patient, with the examinations separated by a prescribed number of hours based on the age of the patient. Confirmatory tests are often used to shorten the required time interval between clinical examinations when time is an issue, as in cases where organ donation is a consideration.

Box 3.1 Testing the respiratory response

- Ventilate patient with 100% O_2 for 10 minutes.
- Check an arterial blood gas to assure normal parameters (with high PaO_2) at onset of test.
- Disconnect ventilator; allow passive flow of oxygen
- Observe patient for 10 minutes—assessing for any sign of respiratory attempt.
- Check another arterial blood gas to assure that PCO_2 has risen above 60 mmHg (a level adequate to stimulate respiratory effort).
- Absence of respiratory effort in presence of PCO_2 above 60 mmHg is consistent with brain death (if all other brainstem reflexes and higher cortical function are absent)

Excessive daytime sleepiness

- Epworth sleepiness scale (see box) is a useful tool in the clinic to assess the common complaint of sleepiness.
- Anyone with sleepiness causing problems with work and driving or an Epworth score of >12 despite having >7 hours sleep each night should be investigated. See Box 3.2.

Causes of persistent sleepiness

- Lack of sleep:
  - Inadequate time in bed
  - Environmental sleep disruption, e.g., babies
  - Shift work
- Sleep disruption (nonenvironmental):
  - Obstructive sleep apnea/hypopnea syndrome (OSA/HS)
  - Periodic limb movement disorder
- Sleepiness with normal sleep:
  - Narcolepsy
  - Idiopathic hypersomnolence
  - Neurological causes, e.g., tumors of hypothalamus, pineal, upper brainstem, bilateral paramedian thalamic infarcts, head injury, MS
  - Drugs
  - Psychological, e.g., depression, seasonal affective disorder

Causes of intermittent sleepiness

- Kleine–Levin syndrome (episodic disorder associated with bulimia, hypersexuality)
- Catamenial hypersomnia

Obstructive sleep apnea/hypopnea syndrome (OSA/HS)

- Commonest cause of sleepiness most often found in middle-aged and elderly men.
- Incidence: 20–50/100,000
- Risk factors:
  - Fifty percent are obese.
  - Retrognathia—results from excessive relaxation of the upper airway muscles during sleep.
- Sleep fragmentation is due to repeated cycles of apnea and arousal.
- Result is increased risk of hypertension, cardiac arrhythmias, and heart failure. Increased risk of motor vehicle accidents (sixfold).
- Investigations include a polysomnogram (PSG). Include esophageal pressure monitoring if upper airway resistance is suspected. Follow with multiple sleep latency test (MSLT) for confirmation of hypersomnolence or if narcolepsy suspected.
- Assessment:
  - History: snoring, witnessed apneas, headaches, daytime and situational somnolence, caffeine use, bruxism
  - Examination: Mallampati score (see Box 3.3), neck circumference, body mass index (BMI), dental occlusion

Box 3.2 Epworth Sleepiness Scale

Name: Date:

Your age: (y) Your sex: M/F

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently, try to work out how they would have affected you.

Use the following **scale** to choose the most appropriate number for each situation:

- 0, would never doze
- 1, slight chance of dozing
- 2, moderate chance of dozing
- 3, high chance of dozing

Situation	*Chance of dozing*
Sitting and reading ……	–
Watching TV ……	–
Sitting, inactive in a public place (e.g., a theatre or a meeting) ……	–
As a passenger in a car for an hour without a break ……	–
Lying down to rest in the afternoon when circumstances permit ……	–
Sitting and talking to someone ……	–
Sitting quietly after a lunch without alcohol ……	–
In a car, while stopped for a few minutes in traffic ……	–
Total ……	–

Score

- 0–10, normal range
- 10–12, borderline
- > 12/24 = abnormal

Used with permission of American Academy of Sleep Medicine, from Johns MW (1991). A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* **14**:540–545; permission conveyed through Copyright Clearance Center, Inc.

Box 3.3 Mallampati score

In sitting position, patient is asked to open mouth widely and protrude tongue to full extent, without phonation.

Class 1: Full visibility of tonsils, uvula, and soft palate

Class 2: Visibility of hard and soft palate, upper portion of tonsils and uvula

Class 3: Soft and hard palate and base of the uvula are visible

Class 4: Only hard palate visible

- Management:
  - Weight loss
  - Reduction of alcohol intake
  - Continuous positive airway pressure (CPAP) is first-line treatment. BiPAP, dental appliances, and surgery may be considered.

Narcolepsy

- Classical tetrad:
  - Sleepiness
  - Hypnagogic hallucinations
  - Sleep paralysis
  - Cataplexy
- Onset in teens or 20s. Incidence: 0.2/100,000
- Cause may be related to a reduction of hypocretin production from the hypothalamus.
- Sleepiness is characterized by irresistible sleep attacks in inappropriate situations such as while eating.
- Cataplexy is due to a sudden loss of muscular tone—resulting in fall to the ground or head drop. Facial twitching may occur. Episodes last a few seconds but may be as long as 10 minutes. There is no loss of awareness. Triggers include emotional outbursts such as laughing. Reflexes are absent during cataplectic episode and present when episode is over.
- Ninety percent of narcoleptic patients are HLA DQB1*0602 (However, this is present in at least 20% of the normal population and lacks diagnostic specificity—cannot be used for diagnosis.)
- Multiple sleep latency test (MSLT) is the most useful investigation. It must be performed on the day following a PSG.

Treatment

- Sleepiness:
  - Scheduled naps
  - Modafinil
  - Adrenergic stimulant drugs
- Cataplexy:
  - Tricyclic compounds (clomiprimine, imiprimine, protriptyline)

- Selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, paroxetine, sertraline) and nonselective serotonin reuptake inhibitors (NSRIs) (venlafaxine)
- GHB (gamma hydroxybutyrate)

Periodic limb movement disorder

- Recurrent limb movements every 20–40 seconds during non-REM sleep. Often reported by bed partner. Quantified on PSG.
- May be associated with daytime sleepiness.
- Associated with restless legs syndrome, which responds to iron supplementation (to raise ferritin above 50 ng/mL), dopamine agonists, and levodopa preparations.

Tremor

- Definition: rhythmical, involuntary oscillatory movement of a body part
- Normal physiological tremor 5–12 Hz (anxiety, caffeine, increased T4)

Phenomenological classification

- Rest tremor
- Action tremor—produced by voluntary contraction of muscle.
  - Postural tremor: present while maintaining posture against gravity
  - Kinetic tremor—occurs during voluntary movement
  - Intention tremor—occurs with target-directed movement with increase in amplitude at termination of movement (cerebellar)
  - Task-specific tremor, e.g., writing tremor
  - Isometric tremor, e.g., orthostatic tremor

Essential tremor

- Sporadic or autosomal dominant:
  - Gene ETM1 on chr3q13 and ETM2 on chr2p22–25
  - DAT scan may differentiate between ET and parkinsonian tremor

Clinical features

- 50% + FH
- Bilateral
- Symmetrical
- Postural or kinetic tremor of hands (e.g., holding a cup)
- Associated with head tremor and/or voice tremor
- Fifty percent respond to alcohol
- Slowly progressive

Differential diagnosis

- Dystonic tremor (asymmetric, irregular)
- PD
- Hyperthyroidism
- Neuropathic tremor

Management

- Propanolol and primidone: singly or in combination

- Anticonvulsants (topiramate and gabapentin)
- Botulinum toxin for refractory cases
- Stereotactic surgery (lesional or deep brain stimulation) to VIM nucleus of thalamus may also be considered in severe cases.

Dystonic tremor

Presentation

- Jerky irregular action tremor
- Task-specific, e.g., writer's cramp with jerky spasms

Management

- Botulinum toxin under electromyogram (EMG)
- Anticholinergic drugs
- Propranolol and primidone

Task-specific tremor

- Localized essential tremor, e.g., primary writing tremor
- Affects writers, musicians, sports persons (golfers, dart players)

Consider:

- Beta-blockers
- Anticholinergics
- Botulinum toxin

Holmes tremor (rubral, midbrain, thalamic tremor)

- Irregular low-frequency tremor at rest, posture, and intention
- Involves proximal and distal arm muscles
- Site of lesion: thalamus to midbrain
- Causes: stroke, AVM, tumors, demyelination
- May respond to L-dopa or dopamaine agonist (DA). Surgery as for ET

Primary orthostatic tremor

- Presentation with unsteadiness on standing
- Improves with walking
- May be associated with cerebellar degeneration
- Frequency 14–18 Hz
- Tremor palpated or auscultated over calf muscles ("helicopter rotor blades"). In late stages, tremor may involve arms.
- Response to medication (clonazepam, gabapentin, L-dopa) variable

Neuropathic tremor

Usually with demyelinating neuropathy:

- AIDP, CIDP
- IgM paraproteinemic neuropathy
- HMSN I
- Porphyria (paroxysmal tremor)

Characteristically an action tremor similar to ET. Research positron emission tomography (PET) studies indicate cerebellar activity.

Drug-induced tremor

- Alcohol
- Salbutamol

- Lithium
- Steroids
- Cyclosporin
- Sodium valproate

Palatal tremor (low frequency 1–2 Hz)

Site of pathology is Guillain–Mollaret triangle formed by red nucleus, olives, and dentate nucleus.

- Essential (associated with clicking heard by patient due to contraction of tensor veli palatini in Eustachian tube)
- Symptomatic:
  - Tumors
  - Whipple disease
  - Neuroferritinopathy
  - Demyelination

Psychogenic tremor

- May be sudden onset
- Unusual combinations of rest and postural/intention tremor
- Decrease in amplitude and frequency with distraction
- "Entrainment"—change in frequency during voluntary contraction or movements of contralateral hand
- External loading increases amplitude (decreased in PD and ET with loading)
- Coactivation—resistance to passive movement with change in tone and tremor
- Past history or other features of somatization or conversion disorder

Tics

- Rapid, stereotypic involuntary movements
- Can be voluntarily suppressed but suppression leads to build up of internal tension
- Triggered by stress or boredom
- Male preponderance (3:1)
- Peak age of onset around 7 years
- Causes:
  - Gilles de la Tourette syndrome
  - Neuroacanthocytosis
  - Neuroleptics
  - Common in Asperger patients
  - Head trauma

Patients present with the following:

- Motor tics:
  - Eye winks
  - Eye blinks
  - Grimaces
  - Head tosses
  - Sniffs

  - Throat clearing
- Vocal tics:
  - Foul utterances (coprolalia)
  - Repeating sounds or words (echolalia)

Resolution usually occurs at the end of adolescence.

Treatment

- When mild, no treatment
- If socially disabling:
  - Dopamine antagonists (fluphenazine, pimozide, tetrabenazine)
  - Neuroleptics, but side effect of tardive dyskinesia
  - Clonidine
  - Reserpine
- With attention-deficit/hyperactivity disorder (ADHD)
  - Stimulants
- With obsessive-compulsive disorder (OCD)
  - SSRIs
- With behavioral concerns/rage issues
  - Alpha adrenergic agonists (clonidine)
- For refractory cases
  - Botulinum injection

Chorea and athetosis

- Chorea: continuous flow of irregular, brief, jerky, flowing movements
- Athetosis—slower, flowing movements
- May be incorporated into semi-purposeful movements

Causes

- Hereditary:
  - HD
  - Benign hereditary chorea
  - Neuroacanthocytosis
  - Wilson disease
  - Spinocerebellar ataxia (SCA)
  - Ataxia telangiectasia
  - Mitochondrial disease (Leigh disease)
- Infection:
  - Sydenham chorea (poststreptococcal)
  - HIV
  - SSPE
  - vCJD
- Vascular (often hemichorea):
  - Infarction
  - Polycythemia
- Metabolic:
  - Hyper- and hypoglycemia
  - Hyperthyroidism
  - Hypocalcemia

- Immunological:
  - Systemic lupus erythematosus (SLE)
  - Anti-phospholipid syndrome
  - Pregnancy—chorea gravidarum
- Drug-induced:
  - Anti-Parkinsonian drugs
  - Dopamine antagonists drugs, e.g., phenothiazines
  - Oral contraceptive (previous history of Sydenham chorea)
  - Amphetamines, cocaine

Treatment

- Neuroleptics, e.g., risperidone, olanzapine.
- Dopamine antagonist—tetrabenazine
- Amantidine
- Anticonvulsants (valproic acid, carbamazepine, phenobarbital)

Myoclonus

Sudden shock-like involuntary movement:
- Positive myoclonus: brief muscle contraction
- Negative myoclonus: pause in muscle activity (asterixis)

Classification

- Distribution:
  - Generalized
  - Focal
  - Multifocal
  - Segmental
- Clinical presentation:
  - Spontaneous
  - Action
  - Reflex (auditory, visual, or to touch)
- Site of origin:
  - Cortical
  - Brainstem
  - Spinal cord

Etiology

Physiological
- Hypnic jerks
- Hiccup

Epileptic
- Focal epilepsy
  - Epilepsia partialis continuans (EPC)
- Myoclonic epilepsies:
  - Progressive myoclonic epilepsy (Unverricht–Lundborg disease)

Encephalopathies
- Metabolic (liver, renal failure)
- Infections
  - Prion diseases
  - HIV
  - Subacute sclerosing panencephalitis (SSPE)
  - Postanoxic
- Drugs, e.g., tricyclics, L-dopa

Degenerative conditions
- Alzheimer disease
- MSA
- Corticobasilar degeneration
- Cerebellar degeneration—Ramsay Hunt syndrome (e.g., celiac disease)

Hereditary
- HD
- Mitochondrial disorders
- Myoclonic dystonia (DYT 11)
- Storage disorders:
  - Lafora body disease
  - Sialidosis
  - Ceroid-lipofuscinosis (Batten, Kuf disease);
  - Lipidosis (Tay–Sachs, Krabbe disease).

Focal lesions of brain or spinal cord

Cortical myoclonus
- Myoclonic jerks triggered by movement or stimulus sensitive
- Distal muscles most affected
- EEG may be diagnostic:
  - Cortical discharges time-locked to myoclonic jerks
  - Giant cortical somatosensory-evoked potentials

Brainstem myoclonus
- Bilateral synchronous jerking with adduction of arms, flexion of elbows, flexion of trunk and head
- Stimulus-induced: tap nose, lip, head, or loud noise

Etiology
- Paraneoplastic
- Brainstem encephalitis
- MS
- Encephalomyelitis with rigidity

Spinal myoclonus
- Rhythmic, repetitive, bilateral, jerking one or two adjacent parts. Persist during sleep
- Propriospinal myoclonus:
  - Usually trunk muscles—flexion
  - Prominent when lying down
  - Stimulus sensitive

Etiology
- Inflammatory cord lesion
- Tumor
- Trauma

Treatment of myoclonus
- Clonazepam
- Sodium valproate
- Piracetam or levetiracetam

Dystonia

Syndrome caused by sustained muscle contraction resulting in twisting and repetitive movements or postures that are due to co-contraction of antagonistic muscles.
- Focal dystonia: one body part
- Segmental: two or more adjacent body parts

Classification
- Primary dystonias. Dystonia and dystonic tremor are the only clinical manifestation.
  - DYT1 dystonia (see "Movement Disorders and Ataxia," p. 256)
  - Sporadic, usually adult onset
- Dystonia plus syndromes:
  - Dopa-responsive dystonia (DRD) (see "Movement Disorders and Ataxia," p. 257)
  - Myoclonic dystonia
- Heredodegenerative syndromes:
  - Wilson disease
  - HD (see "Movement Disorders and Ataxia," p. 252);
  - SCA (see "Movement Disorders and Ataxia," p. 263)
  - Lubag (dystonia–parkinsonism)
  - Early-onset PD (PARKIN 2); (see "Movement Disorders and Ataxia," p. 237)
  - Hallervorden–Spatz
  - Neuroacanthocytosis (also chorea, orofacial dyskinesias, axonal neuropathy, CPK increased, tongue biting, seizures, and cognitive decline
  - Lesch–Nyhan syndrome
- Degenerative syndromes:
  - PD
  - MSA
  - Progressive supranuclear palsy (PSP)
  - Corticobasilar degeneration (CBD)
- Secondary dystonias:
  - Perinatal trauma/hypoxia
  - Stroke
  - Focal lesions, especially putamen or rostral midbrain

Investigations

- Exclude Wilson disease:
  - Serum copper and ceruloplasmin levels
  - 24-hour urinary copper
  - Slit lamp examination for Kayser–Fleischer rings
- If onset <25 years, check DYT1 gene.
- MRI especially in generalized or hemidystonia dystonia, additional neurological signs
- Consider other genetic tests as above (e.g., HD, SCA).
- Fresh blood preparations for acanthocytes x 3 (neuroacanthocytosis)

Management

- Consider trial of L-dopa in any patient with onset <40 years, especially childhood or adolescent, for dopa-responsive dystonia.
- Anticholinergic drugs, e.g., trihexyphenidyl
- Benzodiazepines
- Baclofen
- If unhelpful, especially in generalized dystonia, consider dopamine antagonists:
  - Tetrabenazine
  - Pimozide
- Thalamic (GPi) deep brain stimulation may be an option.
- Focal dystonia—local botulinum toxin (cervical dystonia, blepharospasm, task-specific dystonias, laryngeal dystonia)

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Chapter 4

Disorders of the peripheral nervous system

Zachary London, MD

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Peripheral neuropathy: introduction and clinical approach

General considerations

- Peripheral neuropathy or polyneuropathy—diffuse peripheral nerve lesion, often symmetrical
- Mononeuropathy—lesion of a single nerve (i.e., median, femoral, or abducens). Often entrapment or trauma
- Mononeuritis multiplex—focal involvement of two or more individual nerves, often asymmetric

Polyneuropathy: clinical manifestations

Age of onset varies, for example

- Childhood—CMT
- Adulthood—Diabetes
- Older adult—Paraproteinemia

Acuity of onset

- Acute—AIDP, porphyria, toxic, tick paralysis, diphtheria, vasculitic
- Chronic—B_{12} deficiency, paraproteinemia, diabetes, most other causes

Symptoms

- Motor symptoms—distal weakness predominates in most neuropathies. Difficulty opening jars, tripping over feet
- Sensory symptoms—may be positive (tingling, burning) or negative (numbness).
  - Paresthesia—spontaneous abnormal sensations, which are not unduly painful
  - Dysesthesia—painful paresthesia
  - Allodynia—painful sensation resulting from a nonpainful stimulus, such as stroking
  - Hyperesthesia—increased sensitivity to a stimulus
  - Hyperalgesia—increased sensitivity to a painful stimulus
- Autonomic symptoms—orthostatic lightheadedness, gastroparesis, sweating abnormalities, erectile dysfunction, tachycardia
- Differential diagnosis by pattern of symptoms
  - **Pattern 1:** Symmetrical proximal and distal weakness with sensory loss. (Consider CIDP, vasculitis.)
  - **Pattern 2:** Symmetrical distal weakness with sensory loss. (Consider diabetes, drugs and toxins, hereditary neuropathies, amyloidosis, paraproteinemia.)
  - **Pattern 3:** Asymmetric distal weakness and numbness. (Consider vasculitic neuropathy, HNPP, infectious neuropathy, multifocal trauma or entrapment.)
  - **Pattern 4:** Asymmetric distal or proximal weakness without sensory loss. (Consider multifocal motor neuropathy, motor neuron disease, inclusion body myositis.)

- **Pattern 5:** Asymmetric proximal and distal weakness with sensory loss. (Consider polyradiculopathy or plexopathy, malignant infiltration, brachial neuritis, HNPP.)
- **Pattern 6:** Symmetric small fiber sensory neuropathy without weakness. (Consider diabetes, Fabry disease, amyloidosis, HIV.)
- **Pattern 7:** Symmetric small and large fiber sensory neuropathy without diabetes. (Consider diabetes, drugs, toxins, paraproteinemia.)
- **Pattern 8:** Marked proprioceptive sensory loss. (Consider paraneoplastic, B_6 toxicity, Sjogren, HIV.)
- **Pattern 9:** Autonomic predominant. (Consider autoimmune, amyloidosis, diabetes, AIDP.)
- **Pattern 10:** Neuropathy with cranial nerve involvement. (Consider Lyme, HIV, AIDP, sarcoidosis, malignant infiltration, Tangier disease, trichloroethylene toxicity, anti-Gd1b neuropathy.)

Signs

- Large-fiber neuropathy
  - Loss of vibration and position sense
  - Diminished or absent reflexes
  - Positive Romberg sign
  - Pseudoathetosis (involuntary movements of the fingers when the arms are held out with the eyes shut)
- Small-fiber neuropathy
  - Loss of pain and temperature sensation
  - Reflexes may be normal. (Ia afferent fibers are large and well myelinated.)
- Cutaneous sensory loss in a stocking-glove distribution
- Foot deformities such as pes cavus, pes planus, or hammertoes may indicate a hereditary neuropathy.
- Nerve thickening may be seen in CMT, leprosy, Refsum disease, amyloidosis, or HNPP.
- Autonomic dysfunction
  - Miosis
  - Orthostatic hypotension (BP supine and erect after 3 minutes)

Diagnosis

Acute neuropathies

- Guillain–Barre syndrome (LP, EMG)
- Vasculitic neuropathy (see later)
- Acute intermittent porphyria (urine porphyrins, RBC porphobilinogen deaminase activity)
- Diphtheria (EMG, throat swab)
- Heavy metal or metalloid poisoning (arsenic, lead, thallium levels)
- Tick paralysis (EMG)

Chronic neuropathies

- Mononeuropathy—entrapment, trauma (EMG)
- Multiple mononeuropathies
  - Vasculitis (ESR, EMG, nerve biopsy)
  - Isolated peripheral nervous system vasculitis

- Polyarteritis nodosa (Hepatitis B and C, HIV, cryoglobulins, ANCA)
- Sjogren (anti SS-A-La, anti SS-B-Ro, salivary biopsy)
- Wegener granulomatosis (ANCA)
- Rheumatoid arthritis (RF)
- HNPP (PMP-22 deletion)

Multifocal motor neuropathy (EMG, anti-GM1)

- Polyneuropathy
  - Diabetes (Oral glucose tolerance test)
  - Nutritional and alcoholic
    - — Vitamin B12 deficiency (B12, methylmalonic acid, CBC)
    - — Vitamin B1 deficiency
    - — Vitamin B6 deficiency or excess
    - — Vitamin E deficiency
    - — Alcoholic
  - CIDP (EMG, CSF showing albuminocytologic dissociation)
  - Sensory neuronopathy (anti-Hu, B6, anti SS-A-La, anti SS-B-Ro, HIV)
  - Paraproteinemia (SPEP, immunofixation, serum-free light chain ratio, quantitative urine Bence Jones, CBC)
    - — IgA or IgG (skeletal survey, bone marrow biopsy, anti-GM1, anti-Gd1a, anti-Gd1b, anti-sulfatide, cryoglobulins)
    - — IgM (anti-MAG, bone marrow biopsy)
  - Paraneoplastic (anti-Hu, chest X-ray)
  - Amyloidosis
    - — Primary (nerve biopsy, fat pad biopsy, rectal biopsy)
    - — Familial (transthyretin mutation)
  - Infectious (serum and CSF titers, PCR, nerve biopsy)
    - — Herpes zoster
    - — CMV
    - — HIV-1
    - — Diphtheria
    - — Lyme
    - — Leprosy
  - Sarcoid (ACE, nerve biopsy)
  - Metabolic
    - — Renal failure (BUN, creatinine)
    - — Hepatic failure (Liver enzymes)
    - — Hypothyroidism (Thyroid function studies)
  - Hereditary (selected)
    - — CMT1A (PMP22 duplication)
    - — CMT1B (P0 mutation)
    - — CMT1x (Connexin 32 mutation)
    - — HNPP (PMP22 deletion)
    - — Refsum (phytanic acid)
    - — Fabry (alpha galactosidase A)
    - — NARP (mitochondrial genetic analysis)
    - — Porphyria (urine porphyrins)
  - Toxic (arsenic, lead, thallium, mercury, n-hexane, organophosphates, tetrodotoxin, saxitoxin)
  - Pharmaceutic (Vincristine, cisplatin, metronidazole, nitrofurantoin, chloroquine, vitamin B_6, amiodarone, phenytoin, dapsone)

Investigations in peripheral nerve disorders

- EMG and nerve conduction studies
  - Can distinguish polyneuropathy from polyradiculopathy or plexopathy
  - Can identify mononeuropathy and mononeuritis multiplex
  - Can distinguish axonal and demyelinating neuropathies
  - Can identify subclinical sensory or motor involvement
  - Can distinguish hereditary from acquired demyelinating neuropathies
- Blood tests (see earlier)
  - First line: 75 gram 2 hour oral glucose tolerance test, B_{12}, TSH, SPEP, immunofixation, ESR, renal and liver function tests
  - Second line: ANA, dsDNA, anti-Ro, anti-La, HIV, Lyme
  - Third line: Others, as suspected (see earlier)
- CSF examination
  - Should be considered when AIDP/CIDP is suspected, but nerve conduction studies are equivocal. High CSF protein with normal cell counts supports this diagnosis
  - Should be considered in any rapidly progressive undiagnosed neuropathy. High CSF protein, pleocytosis, oligoclonal bands suggest a demyelinating or inflammatory process.
  - Should be considered for undiagnosed polyradiculopathy or polycranial neuropathy. CSF should be examined for evidence of malignancy, sarcoidosis, or infection.
- Nerve biopsy (sural, radial, superficial peroneal)
  - Can distinguish normal nerve (Fig 4.9) from one with axonal loss (Fig 4.10), but not indicated for most neuropathies.
  - Most useful when suspecting vasculitis, especially if there is no clear evidence of systemic vasculitis
  - Rarely useful for diagnosing:
    - — Amyloidosis (fat pad and rectal biopsy are preferred)
    - — Hereditary neuropathy (if genetic tests negative) (See Fig 4.11)
    - — CIDP (if NCS and CSF not supportive)
    - — Sarcoid neuropathy
    - — Complications include infection, persistent pain, and numbness

Acquired polyneuropathies

Diabetic neuropathies

Epidemiology: Commonest cause of neuropathy worldwide. Eight percent have neuropathy at diagnosis; 50% after 25 years.

Diagnosis

- Diabetes = fasting glucose >126, 2 hr postprandial glucose of 200 mg/dL
- Impaired fasting glucose = fasting glucose 100–125 mg/dL
- Impaired glucose tolerance = 2 hr postprandial glucose 140–199 mg/dL

Classification of diabetic neuropathies

- Diabetic polyneuropathy
  - Length dependent, painful sensory > motor neuropathy
  - Autonomic dysfunction is common.
  - Nerve conduction studies show length-dependent axonal polyneuropathy. May be normal if only small fibers involved.
  - Treatment is foot care, control of hyperglycemia, and medications for neuropathic pain (i.e., gabapentin, nortriptyline, duloxetine, pregabalin).
- Diabetic neuropathic cachexia
  - Fulminant painful neuropathy associated with weight loss and depression
  - Usually in older men with new onset or poorly controlled diabetes
  - Spontaneous recovery with good diabetic control
- Diabetic amyotrophy
  - Clinical manifestations
    - — Abrupt onset of severe pain in backs, hips, and thighs followed by weakness and wasting of proximal muscles > distal muscles
    - — Usually unilateral, but may progress to be bilateral
    - — Associated with weight loss
  - Differential: Vasculitis, malignant infiltration
  - Investigations
    - — Nerve conduction studies usually show distal sensorimotor polyneuropathy
    - — Needle EMG shows denervation in proximal lower extremity muscles including paraspinals
    - — Consider MRI to rule out structural or infiltrative process causing radiculopathy or plexopathy

    Management
    - — Spontaneous recovery over 1–3 years
    - — Methylprednisolone (1g iv tiw x 1, then qweek x 3, then q2 weeks x 4) may speed recovery
    - — IVIG reported to be beneficial as well
- Diabetic cranial neuropathies
  - Oculomotor (III) palsy—pupil sparing
  - Abducens (VI) palsy
- Diabetic mononeuropathies—prone to entrapment syndromes. Surgery should be considered if motor involvement, but results may not be as good as in nondiabetics.
  - Median at the wrist
  - Ulnar at the elbow
  - Common peroneal at the fibular neck

Guillain–Barre syndrome

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)

- Epidemiology: The most common cause of acute neuromuscular weakness. Annual incidence 1–2/100,000
- Clinical features
  - Two-thirds are preceded by a GI or upper respiratory tract infection (*Campylobacter jejuni, CMV, EBV, haemophilus influenzae, mycoplasma*). Neurologic symptoms begin 5 days to 3 weeks later.

- Ascending weakness. Proximal weakness may occur as well because of root demyelination
- Paresthesias common. Actual sensory loss is variable.
- Progressive over days to weeks, nadir by 4 weeks
- Often associated with back pain
- Involvement of cranial nerves can cause facial and bulbar weakness.
- Up to 25% have respiratory involvement requiring mechanical ventilation.
- Autonomic dysfunction (hypotension, hypertension, cardiac arrhythmia)
- Early loss of reflexes

- Diagnostic studies
  - Nerve conduction studies may be normal early in the course of the disease
  - Progressive prolongation of F-responses, motor latencies, and motor conduction velocities. Conduction block correlates with degree of weakness.
  - Elevated CSF protein (may be normal first few days). Little or no CSF pleocytosis, unless associated with HIV or Lyme.
- Management
  - IVIG 0.4 g/kg/day x 5 days
  - Plasma exchange (2–5 exchanges, depending on the severity of the disease)
  - No benefit from corticosteroids
  - Supportive measures
    - — Follow vital capacity (VC) and negative inspiratory force (NIF). If VC <20 mL/kg (1.5 L for an average adult) or NIF is worse than –30 cm H_2O, transfer patient to the ICU and consider elective intubation. Do not wait for O_2 saturation or PO_2 to drop.
    - — Swallowing assessment
    - — Cardiac monitoring in all patients who are severely affected, at least until they start to improve
    - — Treat neuropathic pain (gabapentin, pregabalin, or tramadol). Avoid tricyclic antidepressants early, which may lower threshold for arrhythmia.
    - — DVT prophylaxis
    - — Bowel regimen for constipation
    - — Physical therapy to prevent contractures and speed recovery of function
- Prognosis
  - Mortality is 5%.
  - Most patients recover over many months.
  - Untreated, about 35% of patients have residual weakness, atrophy, hyporeflexia, and facial weakness.
  - Partial recovery followed by relapse is present in <10% of patients. Recurrence after full recovery is 2%.
  - Poor outcome associated with
    - — Older age
    - — Preceding diarrheal illness

— Rapid deterioration and severe weakness
— Electrically inexcitable nerves and muscle wasting

Acute motor axonal neuropathy (AMAN)
- Little or no demyelination
- Often associated with *Campylobacter jejuni* infection
- A subset of patients will recover rapidly

Acute motor sensory axonal neuropathy (AMSAN)
- Little or no demyelination
- Poorer prognosis than AIDP and AMAN

Miller Fisher syndrome
- Ophthalmoplegia
- Ataxia
- Areflexia
- Associated with GQ1b antibody

Acute sensory neuropathy

Acute pandysautonomia

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Epidemiology: Incidence 0.15/100,000. Prevalence: 1.24–1.9/100,000. Mean age of onset 47 years

Clinical manifestations
- Onset is insidious or acute, and course is progressive or relapsing.
- Weakness
  - Can be both distal and proximal limbs
  - Weakness out of proportion to wasting, especially early (suggests conduction block without axonal loss)
  - Face, extra-ocular muscles, and respiratory muscles usually spared
- No autonomic involvement
- Large-fiber sensory loss, sometimes associated with pseudoathetosis and tremor
- Generalized areflexia
- Thickened nerves

Clinical variants
- Focal or multifocal (monomelic) presentation
- Sensory ataxic variant. May resemble sensory ganglionopathy
- Increased frequency in diabetes, but difficult to diagnose because superimposed axonal neuropathy. Diabetes can also cause elevated CSF protein.
- CNS demyelination with CIDP has been reported.

Investigations
- Nerve conduction studies show prolonged F-responses and prolonged conduction velocities, prolonged latencies, and conduction block with temporal dispersion at nonentrapment sites.
- Denervation on EMG suggests superimposed axonal loss.

- CSF shows elevated protein (although not as uniformly as in AIDP) and normal cell counts. Oligoclonal bands may be positive.
- Differential diagnosis
  - Hereditary: CMT1a, CMT1b, CMT1X, HNPP, Refsum
  - Toxic: Amiodarone, arsenic, hexacarbons
  - Paraproteinemic: myeloma, POEMS, Waldenstrom macroglobulinemia
- Screen for monoclonal gammopathy with SPEP and immunofixation. If present, further investigations are warranted to exclude malignancy. If IgM monoclonal protein is present, screen for myelin-associated glycoprotein (MAG) antibodies, which are treated differently.
- Management (see Fig. 4.1)
- Second line (no RCT data)
  - Azathioprine 2–3 mg/kg/day
  - Mycophenolate 1000 mg BID
  - Cyclosporine 2–3 mg/kg/day
  - Cyclophosphamide, oral 1–2 mg/kg/day or IV 1–3 mg (pulsed)
- If the patient has antibodies to MAG, IVIG and steroids are less likely to work. Rituximab (monoclonal antibody against CD20) shows promise.

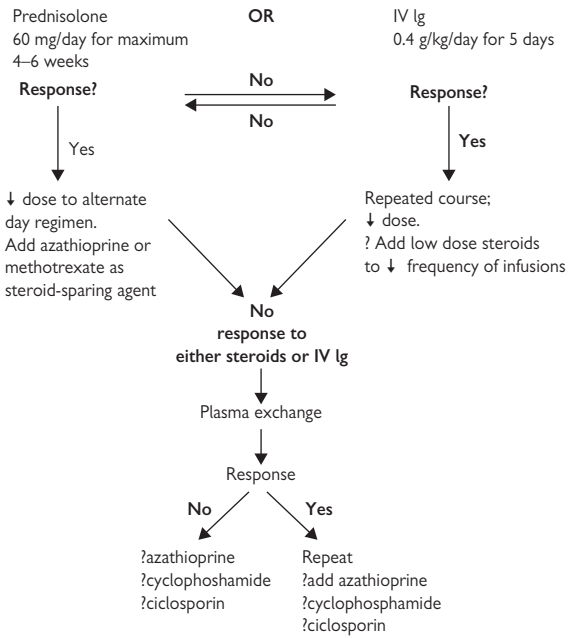

Figure 4.1 Treatment flowchart for CIDP.

Multifocal motor neuropathy with conduction block

Epidemiology: 100 times less common than motor neuron disease. Male:female 3:1. Mean age of onset 41 years.

Clinical manifestations

- Multifocal asymmetric distal weakness
- Hands prominently involved
- No pain or sensory loss
- Cramps and fasciculations may occur
- Weakness > sensory loss (implies demyelination > axonal loss)
- Reflexes normal or diminished in affected limbs
- Rare features: Bulbar weakness, respiratory weakness, myokymia

Investigations

- GM1 antibody titers are high in 20%–80% of cases.
- Nerve conduction studies show low CMAP amplitudes and *conduction block in motor nerves at nonentrapment sites.*
- Denervation changes on needle EMG

Management

- IVIG 1 g/kg at regular intervals (every 2–4 weeks)
- Others: chlorambucil, iv cyclophosphamide, fludarabine, rituximab
- Not effective: Steroids, oral cyclophosphamide, plasmapheresis

Sensory neuronopathy or neuropathy

Clinical manifestations

- Numbness, paresthesias, pain, ataxia, autonomic involvement
- May be distal or generalized
- Normal strength

Differential diagnosis

- Paraneoplastic ganglionopathy
- Sjogren syndrome
- HIV
- Amyloidosis
- Other autoimmune (anti-sulfatide, anti-GD1a)
- Pyridoxine toxicity

Investigations

- Nerve conduction studies show low amplitude SNAPs diffusely
- Laboratory (anti-Hu, B_6, anti SS-A-La, anti SS-B-Ro, HIV, SPEP, anti-sulfatide, anti-GD1a)

Idiopathic autonomic neuropathy

- Clinical manifestations
  - Acute or subacute onset
  - Orthostatic syncope, decreased sweat production, early satiety, erectile dysfunction, bladder dysfunction, constipation
- May be postviral
- CSF protein may elevated, suggesting a GBS-like picture
- Self-limiting with partial recovery expected

Vasculitic neuropathy

Clinical manifestations

- Mononeuritis multiplex or distal symmetric polyneuropathy
- Weakness and sensory loss
- Severe dysesthetic pain, often intractable to neuropathic pain medicines

Differential

- Primary peripheral nervous system vasculitis (no associated systemic disease)
- Polyarteritis nodosa (often associated cryoglobulinemia, hepatitis B or C infection)
- Churg-Strauss syndrome
- Wegener granulomatosis
- Sjogren syndrome
- Rare associations: Rheumatoid arthritis, SLE, systemic sclerosis

Investigations

- Laboratory (ESR, ANCA, HBV, HCV, cryoglobulins, HIV, anti-SSA, anti-SSB, ANA, RF, anti-dsDNA, CCP, C3, C4, CBC, urinalysis, CXR)
- Nerve conduction studies show multiple mononeuropathies, often at nonentrapment sites, or axonal polyneuropathy
- Nerve biopsy—inflammatory cell infiltrates and necrosis in the walls of blood vessels
- Muscle biopsy—same findings, may increase diagnostic yield

Treatment

- Cyclophosphamide 10–15 mg/kg (max 1 g) in pulses (q2 weeks x 6, q3 weeks x 4, then monthly)
- Prednisone 1 mg/kg followed by slow taper. Alternatively, methylprednisolone 1 g pulses with iv cyclophosphamide
- If mild or in remission, consider azathioprine, methotrexate, or mycophenolate.

Neuropathies associated with monoclonal gammopathies

Associated with IgA or IgG monoclonal gammopathies

- Multiple myeloma
- Osteosclerotic myeloma
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma, and skin changes)
  - Light chain is almost always lambda
  - Clinical and EMG changes look like CIDP
- Monoclonal gammopathy of undetermined significance (MGUS)
  - Nonmalignant paraproteinemia found in 1% of normal population
  - Increased frequency in people with idiopathic neuropathy, but cause–effect relationship is uncertain

Associated with IgM monoclonal gammopathies

- Waldenstrom macroglobulinemia
- Antibodies against myelin-associated glycoprotein (MAG)
  - Clinical manifestations:
    — Progressive distal sensory or sensorimotor neuropathy

  - — Sensory ataxia in 50% of patients
  - — Intention tremor
- Diagnostic workup:
  - — Lab: IgM mononclonal gammopathy, elevated anti-MAG titers
  - — EMG/NCV shows severely prolonged latencies with mildly prolonged conduction velocities, suggesting distal demyelination.
  - — Nerve biopsy is diagnostic but usually not necessary.
- Treatment: Rituximab 375 mg/M2 intravenous, qweek x 4, then every 10 weeks

- Monoclonal gammopathy of undetermined significance (MGUS)
  - Neuropathy can be axonal or demyelinating

If monoclonal gammopathy is found during neuropathy workup, it is important to rule out malignancy.

- Laboratory: CBC, BUN/Cr, Ca, 24-hour urine Bence-Jones quantification, serum-free light chain ratio
- Skeletal survey (especially with IgG or IgA gammopathy)
- Consider hematology consult and bone marrow biopsy for:
  - Any IgA or IgM monoclonal gammopathy
  - Any IgG >1.5 g/dL, or increasing on serial SPEPs
  - Abnormal free light chain ratio, 24-hour BJQ, or 24-hour urine protein
  - Abnormalities on skeletal survey
  - Unexplained renal failure, hypercalcemia, anemia, or weight loss

Amyloid neuropathy

Types of amyloidosis

- Primary light chains (patients with primary amyloidosis and plasma cell dyscrasias)
- Transthyretin (patients with hereditary amyloidosis)

Clinical manifestations

- Small-fiber neuropathy
  - Medically intractable pain
  - Autonomic dysfunction
  - Sparing of vibration and position sense
- Carpal tunnel syndrome
- Systemic manifestations: heart failure, nephrotic syndrome, weight loss

Diagnosis

- Pathologic diagnosis: Nerve biopsy, fat pad biopsy, or rectal biopsy
- Laboratory (SPEP, immunofixation, transthyretin gene mutation)

Treatment

- Liver transplantation may help in hereditary amyloidosis
- High-dose chemotherapy and bone marrow transplantation has been reported to help some patients with primary light chain amyloidosis.

Paraneoplastic neuropathy

- Sensory neuronopathy (most common)
- Nonspecific distal sensorimotor neuropathy (less common)
- Motor predominant neuropathy (Hodgkin disease)

Hypothyroid Neuropathy

Clinical manifestations

- Entrapment neuropathies (especially carpal tunnel syndrome)
- Painful paresthesias
- Delayed relaxation of tendon reflexes
- Myoedema with direct percussion of the muscle

Diagnosis

- Abnormal thyroid function studies
- Nerve conduction studies show nonspecific sensorimotor neuropathy.
- CSF protein may be elevated, often >100 mg/dL.

Treatment

- Thyroid replacement is effective.

Acromegalic neuropathy

- Carpal tunnel syndrome and other entrapment neuropathies
- Rare generalized neuropathy with paresthesias and severe weakness

Uremic neuropathy

Clinical manifestations

- Early: Restless legs, muscle twitching
- Dysesthesias, distal weakness

Diagnosis

- Laboratory (BUN, Cr)
- Nerve conduction studies show distal axonal sensorimotor neuropathy.

Treatment

- Peritoneal dialysis may be more effective than hemodialysis.
- Renal transplantation may be effective.

Leprosy

Classification

- Tuberculoid leprosy
  - Small hypopigmented areas with superficial sensory loss
  - Mononeuropathy or mononeuritis multiplex
- Lepromatous leprosy
  - Diffuse proliferation of *M. leprae* bacteria in the nerves, especially in cooler parts of the body
  - Loss of pain and temperature with preserved position sense

Diagnosis—skin biopsy, slit skin smear, or nerve biopsy

Treatment—dapsone, rifampacin

Diphtheric neuropathy

- Clinical manifestations
  - Systemic: Infection of the larynx and pharynx, cutaneous wounds, myocarditis
  - Impaired accommodation
  - Oropharyngeal and ocular paresis
- Diagnosis—throat swab
- Nerve conduction studies show demyelinating neuropathy.
- Prevention—immunization
- Antibiotic treatment may or may not be effective for neuropathy.

HIV neuropathy

Acute demyelinating neuropathy (GBS-like)

- Early in the course of the illness
- Generalized lymphadenopathy
- More frequent involvement of cranial nerves than GBS

Subacute demyelinating neuropathy (CIDP-like)

- Usually predates full blown AIDS
- CSF pleocytosis differentiates it from CIDP
- Treatment: Steroids, IVIG, plasmapheresis

Axonal neuropathy

- Most common type in AIDS patients
- Medically refractory distal dysesthesias

Mononeuritis multiplex—may be associated with CMV infection

Lyme neuropathy

Clinical manifestations

- Painful sensory radiculitis
- Bell palsy (often bilateral)
- Systemic symptoms: Erythema migrans, arthralgias, dilated cardiomyopathy

Diagnosis

- CSF pleocytosis
- Serum *B. burgdorferi* antibodies
- CSF Lyme antigen

Treatment—Ceftriaxone 2g daily or cefotaxime 6g daily

Sarcoid neuropathy

- Cranial neuropathies (most common)
- Polyneuropathy, mononeuritis multiplex, plexopathy, GBS, and pure sensory neuropathy have been described.

Alcoholic neuropathy

- Difficult to distinguish from neuropathy from nutritional deficiency
- Often small fiber predominant (painful with autonomic dysfunction)

Neuropathy caused by heavy metals

Arsenic

- Acute toxicity—GBS-like picture
- Chronic toxicity—painful sensorimotor axonal neuropathy
- Systemic symptoms: Dermatitis, GI disturbance, cardiovascular dysfunction

Lead

- Pure motor neuropathy, especially involving finger and wrist extensors
- May also cause a typical sensorimotor neuropathy

Mercury

- Elemental mercury—sensory > motor neuropathy
- Organic mercury—sensorimotor neuropathy, with motor symptoms predominating

Thallium—small-fiber (sensory and autonomic) neuropathy

Neuropathy caused by drugs: examples

- Cisplatin—pure sensory neuronopathy
- Dapsone—sensorimotor neuropathy or mononeuritis multiplex
- Colchicine—neuromyopathy
- Ethambutol—sensorimotor neuropathy
- Hydralazine—sensorimotor neuropathy
- Isoniazid—coadminister with pyridoxine to prevent sensorimotor neuropathy
- Lithium—sensorimotor neuropathy, postural tremor
- Metronidazole—pure sensory neuropathy or neuronopathy
- Nitrofurantoin—both sensory predominant and motor predominant neuropathy described
- Paclitaxel—sensorimotor neuropathy
- Phenytoin—sensorimotor neuropathy, very rare at standard doses
- Thalidomide—sensory neuropathy or neuronopathy
- Vincristine—pain and small-fiber sensory loss followed by distal weakness

Brachial neuritis

- Also known as neuralgic amyotrophy or Parsonage-Turner syndrome

Clinical manifestations

- Severe pain in the shoulder, followed by weakness and wasting of arm muscles
- Sensory loss is usually inconspicuous.
- May follow the pattern of a plexopathy (20%), mononeuropathy (30%), or multiple mononeuropathies (50%)
- May follow antecedent illness, trauma, surgery, or vaccination

Prognosis—*Spontaneous recovery usually within 3 months to 3 years*

Treatment

- Supportive (pain medicines, including narcotics)
- Steroids may help with pain but do not alter course
- IVIG reported to speed recovery if given very early in course

Radiation plexopathy

- Latent period of 1–2 years or longer
- Weakness and atrophy, usually in proximal upper extremity
- Differentiating radiation plexopathy from tumor recurrence
  - Radiation plexopathy may cause myokymia
  - Radiation plexopathy more likely to affect upper trunk (recurrent breast and lung carcinoma are more likely to affect the lower trunk)
  - Pain much more common and severe in recurrent carcinoma

Hereditary neuropathies

Figure 4.2 shows a flowchart for demyelinating hereditary neuropathies.

Charcot-Marie-Tooth (CMT) disease

Clinical manifestations

- Most present in childhood or adolescence
- Pes cavus or other foot deformities
- Scoliosis
- Slowly progressive distal to proximal weakness
- Sensory symptoms are generally mild.

Classification by nerve conduction studies

- Demyelinating (CMT1)—upper extremity motor nerve conduction velocity <38 m/s. Conduction block and temporal dispersion are rare.
- Axonal (CMT2)—upper limb motor conduction velocities >38 m/s
- Intermediate—upper limb motor conduction velocity 25–45 m/s may indicate CMT1X

Demyelinating neuropathy (CMT1)

- CMT1A is the most common form. AD. 70% caused by *duplication* of the peripheral myelin protein (PMP22) gene on chromosome 17
- CMT1B. Caused by mutation of human myelin protein zero (P0) on chromosome 1
- Dejerine-Sottas disease and congenital hypomyelinating neuropathies, which present in the first decade and are more severe, characterized by point mutations in PMP22, P0, and EGR2.
- CMT1X. Caused by mutation in connexin-32 gene
  - Patchy demyelination with intermediate conduction velocities
  - Women may be affected, but phenotype is less severe.
  - Rare hearing loss or stroke-like episodes with altitude change

Axonal neuropathy (CMT2)

- May be AD or AR
- Fewer genes identified or commercially available for testing
- Mitofusin 2 (MFN2) associated with AD or sporadic neuropathy

Diagnosis

- EMG/NCV can direct laboratory testing by determining if it is axonal or demyelinating.

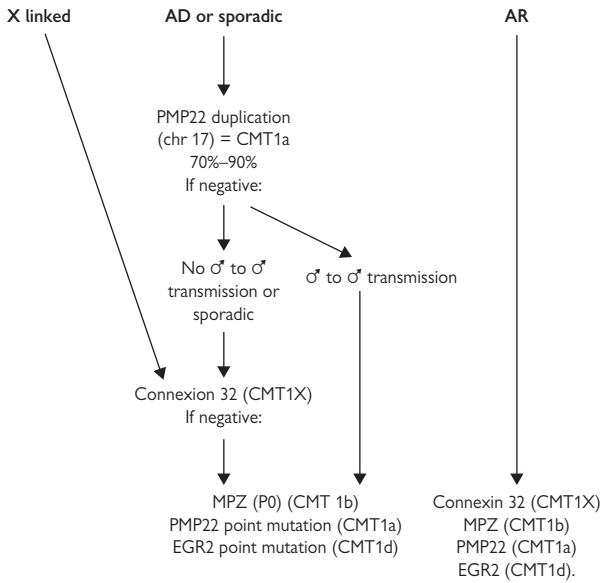

Figure 4.2 Hereditary demyelinating neuropathies.

- Laboratory—gene tests are available for PMP22, connexin 32, P0, EGR2, MFN2, and a few other more rare forms.
- Nerve biopsy—occasionally can be useful in excluding other causes of neuropathy (i.e., Refsum disease, vasculitis).
- CSF protein may be mildly elevated, which can make it difficult to distinguish from CIDP in certain clinical situations.

Prognosis—very slowly progressive. Most do not significantly affect life span.

Hereditary neuropathy with liability to pressure palsies (HNLPP)

AD. Caused by a *deletion* of PMP22 gene on chromosome 17

Clinical manifestations

- Recurrent pressure palsies
- Recurrent brachial plexopathy
- Transient sensory symptoms
- Nerve conductions show patchy demyelination, mild generalized neuropathy

Hereditary sensory and autonomic neuropathies (HSAN)

Clinical manifestations

- Severe sensory loss
- Sensory neurogenic arthropathy (mutilating deformities of the hands and feet)

Classification

- HSAN1—AD, begins in adolescence, SPTLC1 gene or RAB7 gene mutations
- HSAN2—AR, earlier onset, no gene identified
- HSAN3 (Riley-Day Syndrome)—AR, autonomic dysfunction > sensorimotor neuropathy, mutations in IKAP gene
- HSAN4 and HSAN5—AR, mental retardation, anhidrosis, self-mutilating behavior, mutations in TRKA gene

Other hereditary conditions associated with neuropathy

- Leukodystrophies (MLD, adrenoleukodystrophy, adrenomyeloneuropathy, Krabbe disease, Pelizaeus-Merzbacher disease, Cockayne syndrome)
- Friedreich ataxia
- Acute intermittent porphyria (abdominal pain, psychiatric manifestations)
- Familial amyloidosis
- Abetalipoproteinemia
- Tangier disease
- Fabry disease
- Polyglucosan body disease (Lafora body or adult forms)
- Some hereditary ataxias

Mononeuropathies

Facial mononeuropathy (Bell palsy)

- Weakness: Upper and lower face, inability to close the eye, mouth drawn to the affected side (See Fig 4.3)
- Sensory loss: None
- Decreased tearing, hyperacusis, and loss of taste to the anterior two-thirds of the tongue may be present.
- Onset is sudden, usually over hours.
- EMG/NCV are rarely necessary to make the diagnosis, but can be used to determine prognosis.
- Differential diagnosis: HIV, Lyme, facial tumor, sarcoidosis, Melkersson-Rosenthal syndrome

Treatment

- Artificial tears, protective goggles, eye patch at night
- Prednisone 25 mg bid x 10 days
- Anti-virals probably not beneficial

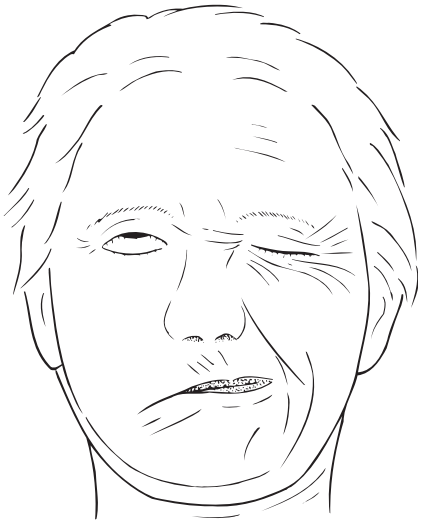

Figure 4.3 Right facial mononeuropathy. The patient has been asked to close her eyes and retract the corners of her mouth. (From Brodal [2003]. *Central Nervous System: Structure and Function*. Used with permission of Oxford University Press.)

Prognosis

- Eighty-five percent have some recovery within 3 weeks.
- Seventy-one percent have complete recovery.

Median mononeuropathy

At the wrist (carpal tunnel syndrome)

- The most common mononeuropathy of the upper extremities
- Weakness: Thumb abduction and opposition
- Sensory loss: Palmar aspect of digits 1, 2, 3, and half of 4. The thenar eminence will be spared.
- Nocturnal paresthesias
- Tinel sign at the wrist, Phalen sign
- Associated conditions: Repetitive use, diabetes, pregnancy, amyloidosis, hypothyroidism, acromegaly, rheumatoid arthritis, dialysis, obesity, menopause
- Treatment: Wrist splints, corticosteroid injections, carpal tunnel release surgery

Anterior interosseous branch

- Weakness: Thumb flexion, flexion of digits 2–3, forearm pronation (mild)
- Sensory loss: none
- Causes: Direct injury, neuralgic amyotrophy (brachial neuritis)

Proximal median mononeuropathy

- Weakness: Weakness of all muscles affected in median mononeuropathy at the wrist and anterior interosseous mononeuropathy, plus wrist flexion and more weakness of forearm pronation.
- Sensory loss: The first four digits and the thenar eminence

Ulnar mononeuropathy

At the elbow

- The second most common mononeuropathy of the upper extremities
- Weakness: Interossei, flexion of digits 4 and 5, ulnar wrist flexion
- Sensory loss: Dorsal and palmar aspects of digits 4 and 5
- Tinel sign at the elbow
- Elbow pain may be present
- Investigations: Nerve conduction studies, ultrasound
- Treatment: A soft foam elbow pad, avoid pressure on elbow, ulnar decompression or transposition (less effective than carpal tunnel surgery)

At the wrist

- Weakness of first dorsal interosseous only, or all interossei, depending on the location of the lesion
- Sensory loss: Usually none. If present, it will only be on the dorsal aspect of the digits 4 and 5.

Radial mononeuropathy

Posterior interosseous

- Weakness: Finger extension, relative sparing of wrist extension. Thumb abduction may be mildly weak because the posterior interosseous nerve supplies the abductor pollicis longus.
- Sensory loss: None
- Pain with extension of the middle finger may be present
- Treatment: Surgical decompression

At the spiral groove

- Weakness: Finger extension, wrist extension, elbow flexion (from brachioradialis weakness), and thumb abduction
- Sensory loss: The lateral dorsum of the hand and thumb, and the dorsal proximal phalanges
- Reflexes: The brachioradialis reflex will be diminished, but the biceps and triceps reflexes will be spared.
- Most common cause is trauma or compression. "Saturday Night Palsy"
- Treatment: Usually conservative, with physical therapy, wrist splinting, and pain management

At the axilla

- Weakness: All muscles affected by radial mononeuropathy at the spiral groove, plus the triceps
- Sensory loss: The lateral dorsum of the hand and thumb, as well as the posterior arm and forearm
- Reflexes: Both triceps and brachioradialis reflexes will be diminished.
- Causes: "Crutch palsy," trauma

Axillary mononeuropathy

- Weakness: Shoulder abduction and external rotation (deltoid and teres minor)
- Sensory loss: Lateral aspect of the shoulder
- Shoulder pain is common.

Suprascapular mononeuropathy

- Weakness: Shoulder abduction and external rotation (supraspinatus and infraspinatus)
- If lesion is at the spinoglenoid notch rather than the suprascapular notch, only the infraspinatus will be affected.
- Sensory loss: None
- Shoulder pain is common.

Long thoracic mononeuropathy

- Scapular winging
- Sensory loss: None
- Shoulder pain is common.
- Treatment is usually conservative, although there have been some reports of improvement with long thoracic neurolysis.

Peroneal mononeuropathy

- Common peroneal mononeuropathy at the fibular neck is the most common.
- Weakness: Ankle dorsiflexion, foot eversion, toe extension
- Sensory loss: Dorsum of the foot and lateral shin
- "Steppage gait"
- Causes: External pressure from prolonged lying (surgery, prolonged hospitalization), direct trauma, weight loss
- Treatment: Avoid crossing legs, extra cushioning around knee while sleeping, AFO brace for foot drop

Sciatic mononeuropathy

- Weakness: All foot, ankle and toe movements, knee flexion
- Sensory loss: Lower extremity below the knee, sparing the medial aspect of the leg (the region supplied by the saphenous nerve)
- Reflexes: Absent Achilles
- Causes: Trauma, neoplasm, iatrogenic from intramuscular injections into the buttock
- Prognosis: Spontaneous recovery, partial or complete, occurs in the majority of patients.

Femoral mononeuropathy

- Weakness: Hip flexion (if proximal to the inguinal ligament) and knee extension
- Sensory loss: Anterior thigh and medial thigh, lateral leg below the knee
- Reflexes: Absent patellar
- Causes: Trauma, retroperitoneal hemorrhage, psoas abscess, childbirth, diabetes (as a limited form of diabetic amyotrophy)

Lateral femoral cutaneous mononeuropathy

- Weakness: None
- Sensory loss and paresthesias over lateral thigh
- Causes: Obesity, diabetes, compression from tight-fitting belts, post-partum women
- Treatment: Avoid compression, local anesthetic injection, topical analgesics, nonsteroidal anti-inflammatories. Neurolysis is rarely indicated, but it can be helpful in refractory cases.

Tibial mononeuropathy (tarsal tunnel syndrome)

- Weakness: None clinically. Atrophy of intrinsic foot muscles may be present.
- Sensory symptoms: Aching, numbness, and tingling involving the sole of the foot, the toes, and occasionally the heel.
- True tarsal tunnel syndrome is rare, and it occurs almost uniformly after a history of trauma to the foot.

Disorders of neuromuscular junction: myasthenia gravis

Epidemiology

Occurs in 50–125/1,000,000. Bimodal distribution, often affecting females in their second and third decades, and males in their sixth and seventh decades.

Pathophysiology

- Autoimmune disease with antibodies against acetylcholine receptor, results in ↓nicotinic ACh receptors at NMJ
- End-plate potentials (EPPs) have ↓amplitude and do not trigger a muscle action potential. With repeated contractions, more fibers fail to contract, leading to fatigue.
- Thymus is abnormal in 75% of cases (15% thymoma, 85% thymic hyperplasia).
- May be associated with other autoimmune diseases: thyroiditis, Graves disease, RA, SLE, pernicious anemia, Addison disease, vitiligo.

Clinical manifestations

- Fatigable weakness
  - Diplopia and ptosis are the most common presenting features. In 15%–20%, the disease never progresses beyond ocular muscles.
  - Bulbar weakness, limb weakness, and respiratory weakness may occur.
  - Weakness may get worse as the day goes on.
  - In patients with longstanding disease, weakness may be fixed.
- No pain, sensory loss, or reflex abnormalities
- Symptoms exacerbated by
  - Superimposed infection
  - Surgery
  - Hyperthyroidism (found in 3%)
  - Drugs that affect neuromuscular transmission
  - Anesthetics that cause neuromuscular blockade
  - Antibiotics (aminoglycosides, quinolones, some macrolides, possibly penicillins)
  - Antihypertensives (beta blockers, verapamil)
  - Anti-arrhythmic drugs (quinine, procainamide)
  - Other: magnesium, phenothiazines, chloroquine, lithium, some anti-epileptics, iodinated contrast agents
  - Penicillamine can cause a drug-induced myasthenic syndrome in people without autoantibodies.

Investigations

Laboratory

- Acetylcholine receptor antibodies (ARAB) present in 85% of patients with generalized MG and 50% of patients with ocular MG.
- A subgroup of ARAB-negative patients will have antibodies to muscle-specific kinase (MUSK) instead.
- Striated muscle antibody occurs in 90% of patients with MG and thymoma, compared to 30% in all MG patients.
- Consider screening for associated autoimmune diseases with thyroid function studies, thyroid antibodies, vitamin B_{12}, and intrinsic and gastric parietal cell antibodies.

Electrodiagnostic testing

- Repetitive stimulation of CMAP shows decrement at rest. After brief exercise, the decrement repairs, and then gradually worsens over 3 minutes. Sensitivity 50%–60%, better with proximal muscles.
- Single-fiber EMG shows increased jitter and blocking (90% sensitive, but specificity is not as high).

Edrophonium (Tensilon) test

- Edrophonium is a short-acting cholinesterase inhibitor.
- An easily testable muscle must be affected, often the deltoid, finger extensors, or levator palpebrae. The latter is especially useful in a neuro-ophthalmology office, where degree of ptosis can be quantified.

- Prepare two syringes. One has 1 mL of saline, and one has 10 mg of edrophonium in a 1 mL solution.
- Inject the saline first and observe for 1 minute, looking for improvement in strength.
- Inject 2 mg of the edrophonium. If no improvement after 1 minute, inject the remaining 8 mg. If no improvement after 1 minute, the test is negative.
- Atropine (0.4 mg, repeat every 3–10 minutes as needed) can be used to counteract side effects, including asystole, bradycardia, nausea, excessive salivation and lacrimation, increasing weakness and fasciculations.

CT of the thorax with contrast is essential to look for thymic enlargement suspicious for thymoma.

Differential diagnosis

Generalized MG

- Lambert–Eaton syndrome
- Botulism
- Drug-induced myasthenia (penicillamine)
- Congenital myasthenic syndromes (defects in neuromuscular transmission that are not caused by autoimmune disease)
- Inflammatory myopathies
- Motor neuron disease (especially bulbar onset)

Ocular MG

- Thyroid ophthalmopathy
- Mitochondrial disease (progressive external ophthalmoplegia)
- Intracranial lesion (cavernous sinus)
- Wernicke encephalopathy
- Oculopharyngeal muscular dystrophy

Management (See Fig. 4.4.)

Pyridostigmine

- Good first-line agent
- A cholinesterase inhibitor
- Acts within 1 hour with duration about 4 hours
- Starting dose 30–60 mg bid-tid. Titrate to effect (often up to 60 mg five times a day). Higher doses can be used but side effects may be limiting.
- Side effects: GI upset, diarrhea, excessive salivation, fasciculations
- Overdose can cause cholinergic crisis, with increased bulbar and respiratory weakness.
- Side effects can be treated with decreasing the dose, or adding glycopyrrolate 1 mg qd to bid.

Prednisone

- Good second-line agent if pyridostigmine is inadequate.
- Note that about half of patients will initially worsen 7–21 days after steroids are started.
- Start with 10 mg on alternate days, increased every 2 or 3 days to 1–1.5 mg/kg on alternate days.

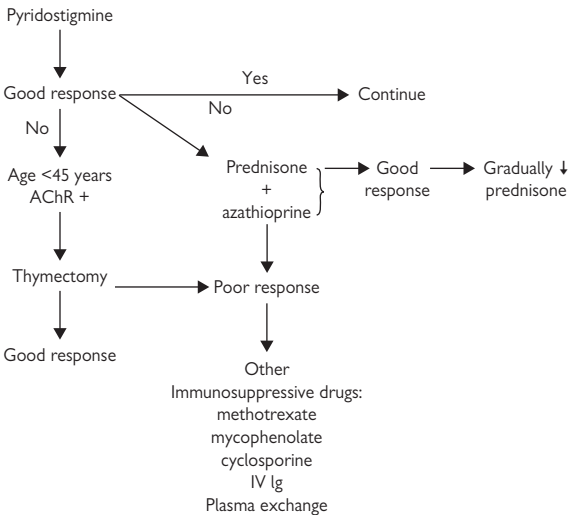

Figure 4.4 Flowchart for the management of MG.

- Improvement begins after 2–4 weeks with maximal benefit at 6 to 12 months.
- After 3 months or when remission is evident, the dose is slowly tapered to the minimum dose required. Often a small dose is required to prevent relapse.
- All patients should be treated for osteoporosis with calcium, vitamin D, and a bisphosphonate.

Other immunosuppressants

- Used when steroids are insufficient or contraindicated, or when steroid side effects are dose limiting. Response may take 3–12 months.
- Follow CBC and LFT every week for 2 months and then every 3 months after that.
- Azathioprine
  - Thiopurine methyltransferase (TPMT) level may predict risk of hematologic side effects.
  - Dose: 50 mg/day for 1 week increasing by 50 mg/week to a goal dose of 2.5 mg/kg/day
  - Side effects: Hypersensitivity reaction, bone marrow suppression, hepatotoxicity

- Cyclosporine
  - Dosages of 2–5 mg/kg/day in two divided doses
  - Side effects: nephrotoxicity, hypertension
  - Monitor trough drug levels
- Cyclophosphamide
  - Reserved for severe cases
  - Oral or intravenous
- Etanercept, rituximab, tacrolimus, and methotrexate have all been reported to be effective.
- Mycophenolate mofetil at 1000 mg bid is commonly used, but it was not shown to be superior to placebo in a 9-month trial.

Plasma exchange

- Indications:
  - Useful in myasthenic crisis with bulbar weakness and respiratory compromise
  - May also be used to reduce perioperative morbidity from thymectomy
  - Rarely, as maintenance therapy when other modalities have failed
- Five to six exchanges over 2 weeks, 2–4 L per exchange.
- Improvement usually noted within days, lasting 1–12 weeks.
- Side effects
  - Bleeding from removal of circulating clotting factors
  - Hypotension and bradycardia
  - Transient electrolyte disturbances
  - Side effects related to need for vascular access (line infections, local thrombosis, vascular perforation)

IV immunoglobulin

- Indications and time course for benefit similar to plasma exchange
- Dose: 400 mg/kg/day for 5 days (total: 2 g/kg)
- If used for maintenance, 1 g/kg q2–4 weeks.
- Side effects
  - Common: headaches, nausea, flu-like symptoms
  - Serious: Renal failure, anaphylaxis, risk of hypercoagulability

Thymectomy

- Indications
  - Thymoma
  - Therapeutic benefit
    - — No good trials, but consensus is that it is helpful in patients under 45 with AChR antibodies
    - — More effective in generalized MG than ocular MG
    - — Benefits may not be evident for months or years after surgery. Can be curative in a fraction of patients
  - Mortality is low in the hands of experienced surgeons
  - Consider pre-operative plasma exchange to reduce the risk of MG exacerbation immediately following surgery.

Women and MG

MG and pregnancy

- Therapy
  - Pyridostigmine and plasma exchange are probably safest.
  - There is a low risk of fetal malformations with prednisone.
  - Azathioprine and mycophenolate are teratogenic.
  - In patients with eclampsia, magnesium sulfate should be avoided if possible.
- Exacerbations during and after pregnancy are common.
- Neonatal MG
- Fourteen percent of babies born to mothers with MG develop neonatal MG due to placental transfer of maternal antibodies.
- Weakness may be apparent days after birth and last for days or months. Treat supportively.

Lambert-Eaton Myasthenic Syndrome

Pathophysiology

- Sixty percent are paraneoplastic, usually associated with small cell lung cancer. Usually, the discovery of LEMS predates the discovery of cancer.
- Forty percent are autoimmune (usually in younger, female patients).
- Both have voltage-gated calcium channel antibody.

Clinical manifestations

- Proximal > distal weakness, often worse in the lower extremities
- Weakness may improve with sustained exercise.
- Reflexes are diffusely low or absent, but may appear after exercise.
- Cranial nerve involvement in about 30% (diplopia, ptosis, dysarthria, dysphagia)
- Autonomic dysfunction (dry mouth, blurred vision, constipation, erectile dysfunction)

Investigations

- On nerve conduction studies, there will be reduced CMAP amplitudes that facilitate >200% with rapid repetitive stimulation (>30 Hz) or after brief intense exercise.
- There may be a decrement on slow (2 Hz) repetitive stimulation.
- Single-fiber EMG may show increased jitter.
- Laboratory
- P/Q voltage-gated calcium channel antibodies
- SOX1 antibodies (50% sensitivity in patients with paraneoplastic LEMS)
- Chest CT or MRI to look for occult tumor. If negative, repeat at regular intervals for 5 years or until tumor is discovered.

Management

- Treat underlying tumor, if present.
- Pyridostigmine
  - Same doses as for MG
  - Usually only partially effective
- Diaminopyridine
  - Blocks potassium channels and prolongs action potentials
  - Dose varies: 5 mg tid to 25 mg qid
  - Side effects: perioral or digital paresthesias, seizures, insomnia
  - An orphan drug in the United States, but it is available on a compassionate-use basis.
- Guanidine
  - 5 mg/kg to 30 mg/kg
  - Side effects: Myelosuppression, renal tubular acidosis, liver failure, cardiac arrhythmias
- Plasma exchange
- IV Immunoglobulin

Botulism

Pathophysiology

- Botulism is poisoning by a toxin produced by *clostridium botulinum*.
- Most commonly comes from inadequately sterilized canned or prepared foods.
- Adult botulism is caused by ingestion of toxin; infantile botulism is caused by ingestion of live bacteria (i.e., in honey).

Clinical manifestations

- Occur 6–48 hours after ingestion
- Difficulty with convergence, ptosis, paralysis of extraocular muscles
- Dilated, poorly reactive pupils, other autonomic dysfunction
- Jaw weakness, dysarthria, dysphagia
- Spreads to trunk and limbs
- Rare cardiac or respiratory involvement

Investigations

- Nerve conduction studies show incremental response with rapid repetitive stimulation, mimicking LEMS
- Laboratory: Serum analysis for toxin by bioassay in mice. (Contact CDC for laboratory locations.)

Management

- Monitor respiration closely, mechanical ventilation if indicated
- Equine serum trivalent botulism antitoxin. Contact State Health Department or CDC
  - Do not wait for positive toxin assay if clinical suspicion is high.
  - Side effects: anaphylaxis (3%), serum sickness (20%)

Myopathy: introduction and clinical approach

Classification

- Inherited
  - Muscular dystrophy
  - Myotonic dystrophy
  - Congenital myopathies
  - Metabolic myopathies
  - Mitochondrial myopathies
  - Channelopathies
- Acquired
  - Inflammatory myopathies
  - Endocrine myopathies
  - Toxic or drug-induced myopathies
  - Metabolic myopathies

Clinical approach to diagnosis

Pattern of weakness

- Limb-girdle weakness
  - Most myopathies
  - Neck flexors and extensors commonly involved
  - Difficulty rising from a chair, climbing stairs, holding arms up to brush teeth, or reaching high shelves
- Distal weakness
  - Examples: Myotonic dystrophy type 1, Miyoshi myopathy
  - Extensor digitorum brevis (EDB) usually spared (contrast with neuropathy, the most common cause of distal weakness)
- Proximal upper extremity, distal lower extremity weakness
  - Examples: Fascioscapulohumeral dystrophy (FSHD), Emery-Dreifuss dystrophy
  - Periscapular muscles of proximal arm, anterior compartment of distal leg (sparing EDB), scapular winging
  - FSHD is often asymmetric.
- Distal upper extremity, proximal lower extremity weakness
  - Example: Inclusion body myositis (IBM)
  - Wrist and finger flexors, quadriceps affected first
  - Face is spared, but dysarthria/dysphagia are common
  - Often asymmetric
- Weakness with ophthalmoplegia
  - Examples: Oculopharyngeal muscular dystrophy (OPMD), Kearns-Sayre syndrome
  - Patients may have ophthalmoplegia without diplopia.
- Isolated neck extensor myopathy
- Facial weakness is seen in FSHD and myotonic dystrophy. (Differential would also include ALS, AIDP, and MG.)

Associated symptoms

- Weakness, fatigue, exercise intolerance, atrophy
- Myalgias are usually orthopedic or rheumatologic in origin, but they may be seen in metabolic myopathies.
- Contractures
  - A fixed tightening of muscles and tendons
  - Electrically silent
  - Seen in Duchenne, Becker, Emery-Dreifuss, paramyotonia congenita
- Myotonia
  - Inability to relax a muscle
  - Seen in myotonic dystrophy, myotonia congenita, paramyotonia congenita, hyperkalemic periodic paralysis
- Myoglobinuria
- Calf pseudohypertrophy is seen in Duchenne, Becker, and some limb-girdle muscular dystrophies. True hypertrophy is seen in myotonia congenita.

Age of onset

- Child—congenital myopathies, Duchenne dystrophy, dermatomyositis
- Young adult or adult—FSHD, polymyositis
- Older adult—IBM, OPMD

Temporal evolution and precipitating factors

- Most myopathies are chronic
- Acute or subacute—toxic (i.e., steroids, statins) or inflammatory myopathy
- Episodic—periodic paralysis
- Exercise induced—metabolic myopathy
- Induced by cold exposure—Myotonic dystrophy, paramyotonia congenita
- After exercise followed by rest—periodic paralysis
- After a large carbohydrate meal—periodic paralysis

Inheritance

- Autosomal dominant
  - FSHD
  - OPMD
  - Limb-girdle dystrophies (type 1's)
  - Myotonic dystrophy
  - Periodic paralysis
- X-linked recessive
  - Duchenne and Becker muscular dystrophy
  - Emery-Dreifuss muscular dystrophy
- Autosomal recessive
  - Limb-girdle dystrophies (type 2's)
  - Metabolic myopathies
- Maternal inheritance—mitochondrial myopathies

Associated signs

- Cataracts, frontal balding—myotonic dystrophy
- Dysmorphic features—congenital myopathy
- Rash—dermatomyositis

- Respiratory insufficiency—Duchenne, acid maltase deficiency, congenital myopathies
- Arrhythmia—Kearns-Sayre syndrome, Emery-Dreifuss dystrophy
- CHF—Duchenne, Becker, acid maltase deficiency, myotonic dystrophy

Investigations

Serum CK

- Highest levels in inflammatory myopathies, acute rhabdomyolysis, early stages of Duchenne dystrophy
- Normal in most congenital myopathies, myotonic syndromes, corticosteroid or thyrotoxic myopathies. Also may be low in very slowly progressive myopathies or if muscle mass is low.
- In asymptomatic individuals, ↑CK may indicate
  - A predisposition to malignant hyperthermia
  - McArdle disease
  - Early inflammatory myopathy
  - Duchenne or Becker carrier status
- Reasons to have high CK other than myopathy
  - Recent strenuous exercise, viral infection, seizures, or surgery
  - Recent EMG (controversial)
  - Motor neuron disease, AIDP (almost never >1000)
  - Larger baseline muscle mass
  - "Idiopathic hyper-CKemia"

Myoglobinuria

- Seen in glycogenoses, lipid disorders, inflammatory myopathies, some limb girdle myopathies
- Also may be found after prolonged exercise, trauma, viral or bacterial infections, heat stroke, or severe metabolic disturbances

The ischemic forearm test

- Venous lactate and ammonia levels are drawn at rest and at 1, 2, 4, 6, and 10 minutes after 1 minute of repetitive isometric contractions of the forearm flexor muscles.
- Normally, there is a 2–3-fold ↑ in lactate concentration within the first 2 minutes after exercise. Lactate will be decreased or absent in certain metabolic myopathies.
  - Myophosphorylase deficiency
  - Phosphofructokinase deficiency
  - Phosphorylase B kinase deficiency
  - Lactate dehydrogenase deficiency
- Ammonia levels will be reduced or absent in myoadenylate deaminase deficiency
- Electrodiagnostic tests
- Rarely diagnostic of a specific myopathy, but can be useful to confirm that muscle is the correct localization and help guide muscle selection for biopsy.
- Nerve conduction studies are generally normal.
- EMG findings

- Positive waves and fibrillations may be seen if there is muscle fiber necrosis, such as in inflammatory myopathies, toxic myopathies, and some muscular dystrophies.
- Myotonic potentials suggest a myotonic disorder.
- Early recruitment with short duration, low-amplitude polyphasic motor units

Muscle biopsy

- In patients a chief complaint of myalgias, normal CK levels, and a normal neurological examination, a muscle biopsy will only diagnose a specific myopathy in 2%.
- Muscle selection
  - A muscle that is clinically affected, but not end-stage. MRC grade 4 is ideal.
  - Select a muscle that has not been the site of an IM injection or EMG study within the last 3 months.
- The choice between needle biopsy and open biopsy depends on experience and availability.
- Some of the muscle tissue obtained should be frozen for histological, histochemical, and immunohistochemical investigations. The latter technique can be used to diagnose enzyme disorders, storage disorders, and various dystrophinopathies and sarcoglycanopathies.
- Tissue should also be fixed in glutaraldehyde for electron microscopy. Useful for diagnosis of mitochondrial myopathies and IBM.
- Pathologic evaluation can distinguish between normal muscle (Fig 4.5) denervation (Fig 4.6) and myopathies such as dermatomyositis (Fig 4.7) and Duchenne muscular dystrophy (Fig 4.8)

Molecular genetic studies

- Utility
  - Only common mutations can be screened.
  - Confirmatory test only
  - May eliminate the need for a muscle biopsy
- Muscular dystrophies
  - Duchenne muscular dystrophy (dystrophin gene)
  - Becker muscular dystrophy (dystrophin gene)
  - Emery-Dreifuss (EMD gene encoding emerin or LMNA gene encoding lamin A and C)
  - Myotonic dystrophy 1 and 2
  - FSHD (deletion in 4q)
  - OPMD (PABP2 gene)
  - Limb-girdle dystrophies (mutations encoding dysferlin, FKRP, myotillin, lamin A/C, caveolin 3, calpain 3, sarcoglycans)
- Mitochondrial disorders
  - Kearns-Sayre syndrome
  - Chronic progressive external ophthalmoplegia (CPEO)
  - MELAS, MERFF, NARP
- Congenital myopathies
  - Central core (RYR1 gene)
  - Multicore (SEPN1 and RYR1 genes)
  - Myotubular myopathy

- Other
  - Myotonia congenita
  - Periodic paralysis
  - Myofibrillar myopathy (desmin gene)

Dermatomyositis and polymyositis

Clinical manifestations of dermatomyositis (DM) and polymyositis (PM)

- Symmetric limb-girdle pattern of muscle weakness, often with involvement of neck and bulbar muscles
- Interstitial lung disease may coexist; 10% associated with Jo-1 antibodies
- Myocarditis and conduction abnormalities may occur
- Presentation is usually acute or subacute over weeks (DM) or may evolve slowly over months (PM)
- In dermatomyositis, rash may precede muscle weakness
  - Heliotrope (blue-purple) rash with edema on upper eyelids
  - Erythematous rash over cheeks, upper chest, upper posterior chest ("shawl sign"), and knuckles
  - Erythematous scaly eruption over knuckles (Grotton sign)
  - Dilated capillary loops at base of fingernails
  - Lateral and palmar areas of hands become rough and cracked with "dirty" horizontal lines ("mechanic's hands").

Investigations (see Table 4.1)

Management

- Corticosteroids
  - Early aggressive management associated with better outcome.
  - Consider induction therapy with iv methylprednisolone 500 mg for 5 days.
  - Oral prednisone 1 mg/kg daily
  - When CK normal and clinical improvement reduce by 5 mg alternate days over 2 months. Thereafter, dose is gradually reduced monitoring CK and clinical state.
  - Osteoporosis prophylaxis with baseline bone scan, bisphosphonate with Ca, and vitamin D supplements
- Other immunosuppressants
  - Azathioprine 2.5 mg/kg/day (Check TPMT levels)
  - Methotrexate (up to 30 mg/week)
  - Cyclosporine up to 5 mg/kg/day
  - Oral cyclophosphamide 2 mg/kg/day
  - Mycophenolate 1 g bid
- IV immunoglobulin
  - 2 g/kg given once a month
- Physical therapy to maintain strength, prevent contractures, and supply orthotics
- OT home visit for advice about home access, stairs, hand rails in the bathroom, etc.

Table 4.1 Inflammatory myopathies

Characteristics	Polymyositis	Dermatomyositis	Inclusion body myositis
Age at onset	>18 years	Any age, 2 peaks: 5–15 and 45–60 years	>50 years
Female:male ratio	2:1	2:1	1:3
Familial association	No	No	Rarely
Association with: connective tissue diseases	Yes	Scleroderma, MCTD	Yes
Systemic autoimmune diseases	Yes	No	No
Malignancy	++	+++ in adult form	+
Viruses	No	HIV, HTLV-1	No
Muscle involvement	Proximal symmetrical	Proximal symmetrical	Distal, proximal, asymmetrical, finger flexors, quadriceps
Atrophy	+	+	++
Serum CK (I)	Up to 50 ×	Up to 50 ×	Normal to 10 ×
EMG	Myopathic	Myopathic	Myopathic + mixed large units; 30% have signs of an axonal neuropathy
Muscle biopsy	Peri- and endomysial infiltrate, inflammatory infiltrate	Perifasicular atrophy Perivascular and perifasicular, inflammatory infiltrate	Endomysial infiltrate rimmed vacuoles
Cells	CD8 + T cells, macrophages	B cells, CD4 + T cells, macrophages	CD 8 + T cells, eosinophillic inclusions
EM		Tubulovesicular inclusions in capillary endothelium	Helical filaments, fibrils

- Monitoring
  - Primarily muscle strength and function rather than CK
  - Steroid-induced myopathy a possible concern. Needle EMG showing abnormal spontaneous activity more suggestive of worsening inflammatory myopathy rather than superimposed steroid myopathy.

Inclusion body myositis

Clinical manifestations

- Painless weakness, progressive over months to years
- Mean age of onset is 60.
- Distribution of muscle weakness is clue to diagnosis
  - Distal upper extremity weakness, especially finger and wrist flexors
  - Marked quadriceps weakness, presenting as falls and difficulty going down stairs
  - Other limb muscles eventually involved
  - Weakness and atrophy may be asymmetric (10%–20%).
  - Mild facial weakness may occur.
  - Dysarthria and dysphagia may occur at any stage of the disease.

Differential diagnosis

ALS

- Both can present with progressive painless asymmetric weakness and dysphagia.
- IBM does not cause upper motor neuron signs.
- EMG shows neurogenic motor units in ALS, and mixed neurogenic/myopathic motor units in IBM.

Polymyositis

- Both can present with symmetric proximal weakness, although this is less common in IBM.
- In those situations, muscle biopsy must be used to distinguish them.

Investigations

- CK levels are normal or elevated, but always <10x the upper limit of normal.
- EMG—positive waves, fibrillation potentials, and motor units that are either myopathic or mixed myopathic/neurogenic.
- Muscle biopsy, showing an inflammatory infiltrate and rimmed vacuoles

Management

- Nothing is clearly effective.
- A trial of corticosteroids may be considered if marked inflammatory cells on biopsy or very high CK, which may suggest PM is the correct diagnosis.
- One small study showed no objective benefit with IVIG, but patients in treatment arm reported improved quality of life.

Inherited myopathies

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD)

Clinical manifestations

- Presentation in early childhood with walking difficulty and toe walking

- BMD is the milder form with better prognosis.
- Calf pseudohypertrophy
- Contractures
- Gower sign (using hand support to push self up from chair or floor)
- Cardiomyopathy and conduction abnormalities
- Scoliosis compromises respiratory function and may result in acute respiratory failure.
- Fractures are frequent.

Investigations

- CK >10,000
- DNA detection of mutation in dystrophin gene found in 70%
- Muscle biopsy
  - Degeneration, regeneration, hypertrophic fibers, and replacement of muscle with fat and connective tissue
  - Dystrophin stains can be performed.
- EMG shows nonspecific myopathic changes
- EKG may show tall right precordial R waves with an increased R/S ratio and deep Q waves in leads I, aVL, and V5-V6.

Management

- Prednisone (0.75 mg/kg) can increase strength, muscle function, and pulmonary function
- Supportive care

Limb-girdle muscular dystrophies (see Table 4.2)

Clinical manifestations

- Range of phenotypes from nonspecific limb-girdle weakness to those resembling X-linked muscular dystrophies
- Facial weakness is absent.
- Variable cardiac and respiratory complications

Distal myopathies

Miyoshi myopathy

- AR, onset in teens
- Weakness and wasting of gastrocnemius muscle progressing to involve more proximal muscles
- CK markedly ↑
- Muscle biopsy shows dystrophic changes.

Welander myopathy

- AD, onset between fourth and sixth decades
- Weakness in the upper limbs (wrist and finger extensors) and wasting of hand muscles followed by foot drop and leg weakness
- CK normal to slightly ↑
- Muscle biopsy shows myopathic changes with rimmed vacuoles.

Nonaka myopathy (hereditary IBM type 2)

- AR
- Onset with tibialis anterior weakness and wasting

Table 4.2 Genetics of limb–girdle muscular dystrophy (LGMD) syndromes

Syndrome	Chromosome	Protein
Autosomal dominant		
LGMD1A	5q	Myotilin
LGMD1B	1q	Lamin A/C
LGMD2C	3p	Caveolin
Autosomal recessive		
LGMD2A	15q	Calpain
LGMD2B	2p13	Dysferlin
LGMD2C	13q	γ-Sarcoglycan

Fascioscapulohumeral muscular dystrophy (FSHD)

Clinical manifestations

- AD, onset usually in teens
- Weakness of face followed by scapular fixators, leading to scapular winging
- Biceps and triceps are weak, but deltoid is spared.
- Leg weakness is common, affecting hip flexors, quadriceps, and tibialis anterior.
- Weakness is usually asymmetric, often worse on the right.
- Risk of being wheelchair bound is 20%.
- No cardiac complications

Investigations

- CK ↑ severalfold
- EMG shows myopathic changes with or without abnormal spontaneous activity.
- DNA diagnosis by demonstration of truncated region at chromosome 4q35.
- Muscle biopsy may show inflammatory changes, confusing the diagnosis.

Emery-Dreifuss muscular dystrophy

- X-linked and AD inheritance
- Progressive scapulo-humeral peroneal weakness with thin muscles
- Early contractures of cervical extensors, biceps, and long finger extensors
- Cardiac conduction defects with atrial paralysis. Absent or small P waves causing sinus bradycardia. Pacing is usually necessary.
- Diagnosis by muscle biopsy with immunohistochemistry to demonstrate absence of lamin A/C and emerin.

Myotonic dystrophy

Genetics

- Autosomal dominant disorder with full penetrance but variable expression
- Anticipation (increased severity with successive generations) is well-recognized.
- Myotonic dystrophy type 1: CTG trinucleotide repeat in the dystrophica myotonica protein kinase (DM-PK) gene
- Myotonic dystrophy type 2: CCTG tetranucleotide repeat in zinc finger gene on chromosome 3

Clinical manifestations

- Phenotype varies from a lethal severe congenital myopathy to late-onset cataracts
- Neuromuscular
  - Myotonia
  - Type 1: Distal muscle weakness (hand and foot drop) with progression to proximal muscles. Ptosis, facial weakness, and weakness of temporalis, masseter, and sternocleidomastoid with wasting
  - Type 2: Limb-girdle pattern of weakness. Face may be involved, but less common than in type 1.
- CNS
  - Somnolence
  - Cognitive impairment
- Cardiac
  - Conduction defects with heart block and tachyarrhythmias due to fibrosis in the conduction system of the SA node
  - Cardiomyopathy, especially late in course
  - Risk of sudden death and anesthetic complications
- Endocrine
  - Diabetes mellitus and impaired glucose tolerance
  - Testicular atrophy
  - Repeated miscarriages and menstrual irregularities
- Smooth muscle weakness
  - Esophageal problems
  - Recurrent cholecystitis
  - Constipation
- Other systemic
  - Frontal balding
  - Cataracts, retinal degeneration

Investigations

- Serum CK may be ↑
- Brain MRI often shows subcortical white matter involvement
- EMG: Myotonic discharges, myopathic motor units
- DNA testing available for both type 1 and type 2

Management

- Genetic counselling, especially as the severe congenital form occurs in the offspring of affected females with >100 repeats.
- Prenatal diagnosis is available
- Mexilitine can treat symptomatic myotonia. Monitor QT interval.

Congenital myopathies

Nemaline myopathy

- Clinical manifestations
  - Onset at birth to adulthood
  - Weakness and hypotonia
  - Congenital onset: Cognitive impairment, arthrogryposis
  - Adult onset: Head ptosis, paraspinal atrophy
- Common mutation in childhood-onset skeletal muscle α-actin
- Investigations
  - CK may be normal or slightly elevated.
  - EMG may show myopathic or neuropathic features (especially severe cases).
  - Muscle biopsy shows nemaline rods.

Central core myopathy

- Clinical manifestations
  - Multiple syndromes with various clinical presentations
  - Most have childhood or congenital onset
  - Hypotonia, proximal weakness (legs > arms), mild facial weakness
  - Malignant hyperthermia
- CK ↑ in central core and malignant hyperthermia patients
- Genetics: various defects in ryanodine receptor protein (RYR1)
- Muscle biopsy: Central cores, internal nuclei (especially in older patients)

Centronuclear (myotubular) myopathy

- Clinical manifestations
  - Onset in infancy, usually death in infancy
  - Proximal and distal symmetric weakness and respiratory insufficiency
- CK usually normal or mildly elevated
- Genetics: various defects in myotubularin gene
- Muscle biopsy shows single central nucleus.

Motor neuron disease

Childhood-onset motor neuron disease

Spinal muscular atrophies (SMA)—all from mutation in survival motor neuron gene on chromosome 5

- Infantile SMA type 1 (Werdnig-Hoffman syndrome)
  - Onset in utero to 6 months
  - Eighty-five percent die by age 2
- SMA type 2
  - Intermediate onset, 6 months–1 year
  - May survive but never walk
- Juvenile SMA type 3 (Kugelberg-Welander syndrome)
  - Slowly progressive gait disorder in late childhood
  - Progressive limb weakness
  - Hyporeflexia, sparing of sensation

- Life span may be relatively normal, since serious bulbar and respiratory weakness are rare.

Fazio-Londe syndrome

- Late childhood or adolescent onset
- Selective dysphagia and dysarthria

Hexosaminidase deficiency

- Autosomal recessive motor neuron disease
- Associated with psychosis, dementia, and cerebellar signs
- More common in patients of Ashkenazi-Jewish descent, especially with known cases of Tay-Sachs disease in the family
- Diagnosis: hexosaminidase levels (white cell enzymes)

Amyotrophic lateral sclerosis

Epidemiology

- Incidence 2/100,000/year; prevalence 5/100,000
- Median age of onset is 60, but up to 10% present <40
- Slight M > F

Genetics

- About 5% of cases are familial in an autosomal dominant pattern.
- Twenty percent of familial cases have a mutation of superoxide dismutase (SOD1).

Clinical manifestations

- Progressive atrophy and weakness
  - Often begins in hands, usually asymmetrically
  - Mixed spastic/flaccid dysarthria
  - Dysphagia
  - Face weakness (usually mild)
  - Neck flexion weakness
  - Respiratory weakness (usually late)
  - Normal extra-ocular movements and bladder function
- Prominent fasciculations in affected muscles, including tongue
- No significant pain or sensory loss
- Upper motor neuron signs (hyperreflexia, extensor plantar responses, Hoffman sign, clonus, brisk jaw jerk)
- Muscle cramps
- Weight loss
- Uvula movements are more vigorous in response to gag reflex than on volitional movement
- Pseudobulbar affect: Emotional lability with inappropriate crying or laughing
- Ten percent are associated with dementia, usually frontotemporal type.

Diagnosis

- Laboratory studies are commonly obtained, but it is extremely rare to find a lab abnormality that can be implicated in a competing diagnosis. Labs may include CBC, basic metabolic panel, CPK, ESR, SPEP/immunofixation, TSH, PTH, RPR, B12, ESR, and ANA.

- Other motor neuron diseases should be ruled out, if clinically suspected.
  - Spinal muscular atrophy (SMN gene)
  - Spinobulbar muscular atrophy (androgen receptor gene)
  - Hereditary spastic paraparesis
  - Primary lateral sclerosis (upper motor neuron only)
  - Infectious MND (West Nile, HIV, HTLV-1, poliomyelitis, other enteroviruses)
  - Prion disease (amyotrophic form of CJD)
  - Toxins (lead, mercury)
  - Endocrinopathies (hyperparathyroidism, insulinoma, hyperthyroidism)
  - ALS-syndrome associated with lymphoma (lymphadenopathy, monoclonal gammopathy, elevated CSF protein, and abnormal bone marrow biopsy)
- Rule out mimics of motor neuron disease, if suspected
  - Structural lesions (MRI)
    - — Cervical myeloradiculopathy
    - — Foramen magnum lesions
    - — Syringomyelia (MRI spine, usually cervical or thoracic)
    - — Spinal dural fistulae
  - Multifocal motor neuropathy with conduction block (nerve conduction studies, anti-GM1 antibodies)
  - Inclusion body myositis (EMG, muscle biopsy)
  - Myasthenia gravis (acetylcholine receptor antibody, repetitive stimulation, SFEMG)
  - Benign fasciculation or cramp-fasciculation syndromes (clinical diagnosis)
  - Vasculitis (nerve biopsy)
- EMG/NCV
  - Nerve conduction studies may show low-amplitude CMAP's in affected muscles
  - Positive waves and fibrillations in at least three of four body segments (cranial, cervical, thoracic, lumbar) without an alternate explanation

Prognosis

- Relentlessly progressive
- Mean duration of symptoms is 4 years.
- Twenty percent of patients live >5 years.

Management

- Involvement of a multidisciplinary team
  - Physical and occupational therapy
  - Dietician
  - Speech and language therapy (communication aids, swallowing assessments)
  - Respiratory therapy
  - Social worker
- Orthotics (neck brace, AFO)
- Drug treatment: Riluzole, 50 mg bid increases life expectancy by 3 months. Monitor LFTs.

- Nutrition
  - Nutritional supplements
  - Consider percutaneous endoscopic gastrostomy (PEG) to decrease risk of aspiration, or in patients with >10% loss of body weight or dehydration
- Respiratory support
  - Symptoms: orthopnea, dyspnea on mild exertion or talking, poor sleep, excessive daytime sleepiness, fatigue, impaired concentration, morning headache
  - Signs: Tachypnea, paradoxical diaphragmatic movement, weak cough, tachycardia, confusion
  - Noninvasive positive pressure ventilation
    — Indicated for FVC <50% predicted or NIF worse than –60 mmH20
    — Start BiPAP at 8/4.
- Symptomatic treatment
  - Cramps: carbamazepine, quinine, phenytoin, baclofen
  - Sialorrhea: home suction decide, atropine eye drops 0.% on drop sublingual bid, hyoscine transdermal patches, amitriptyline 10 mg, glycopyrrolate liquid
  - Emotional lability: SSRI or tricyclic antidepressant
  - Depression: psychological support, antidepressants

Spinobulbar muscular atrophy (SBMA, Kennedy syndrome)

Genetics: X-linked recessive trinucleotide repeat disease

Clinical manifestations
- Onset usually age 40–70
- Dysarthria and dysphagia
- Limb weakness often begins years later
- Tongue fasciculations
- No upper motor neuron signs
- Sensory symptoms are rare.
- Signs of androgen insensitivity
  - Gynecomastia
  - Slightly decreased reproductive fitness
- Increased risk of diabetes

Investigations
- Nerve conduction studies show a large-fiber sensory peripheral axonopathy (usually asymptomatic).
- Androgen receptor gene, >40 CAG repeats for full mutation

Monomelic amyotrophy

Epidemiology: Sporadic, men only, between 15 and 30

Clinical manifestations
- Weakness and wasting of one arm
- Usually begins in C8-T1 myotomes and spreads to involve wrist flexor and extensor muscles over 1–2 years. It then stabilizes.
- No upper motor neuron signs

Investigations

- EMG shows sparse fibrillation potentials in affected muscles.
- MRI of cervical spine may show cord atrophy.

Muscle and nerve pathology

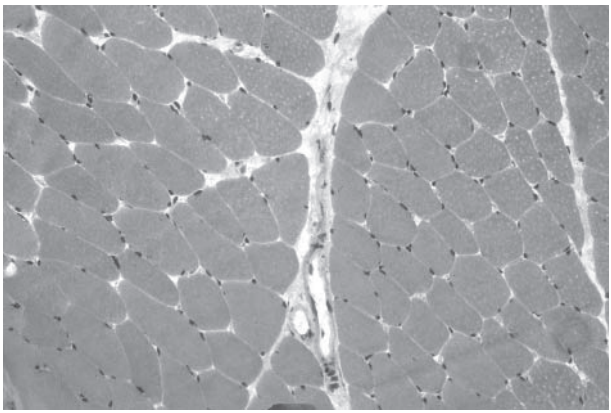

Figure 4.5 Normal muscle. Individual fibers have minimal variation in size.

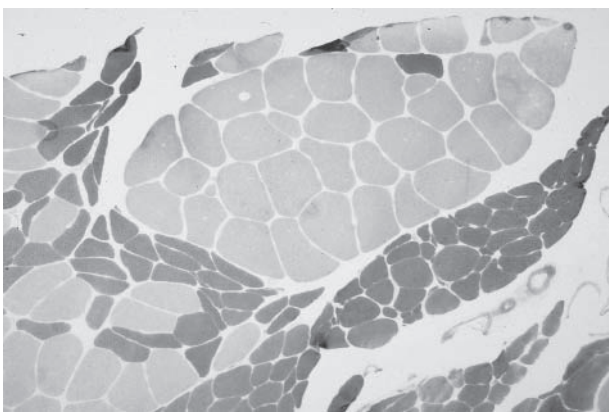

Figure 4.6 Neurogenic muscle biopsy showing angular fibers, fiber type grouping, and group atrophy.

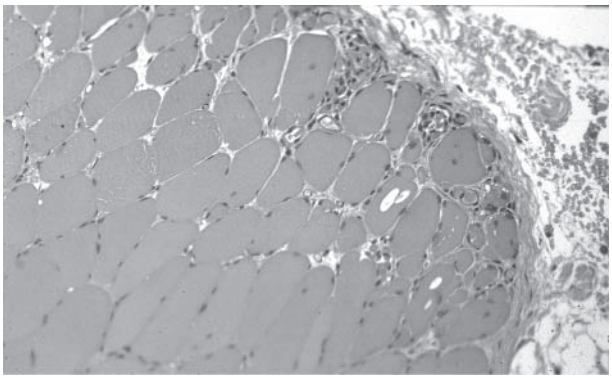

Figure 4.7 Dermatomyositis, showing perifascicular atrophy and an inflammatory infiltrate.

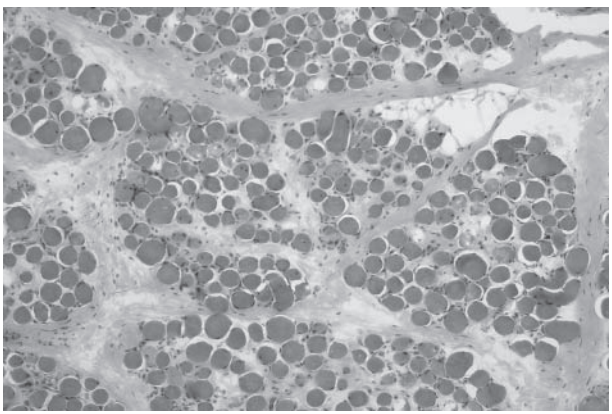

Figure 4.8 Duchenne muscular dystrophy. Muscle largely replaced with fat and connective tissue. Muscle fibers are rounded with variation in fiber size.

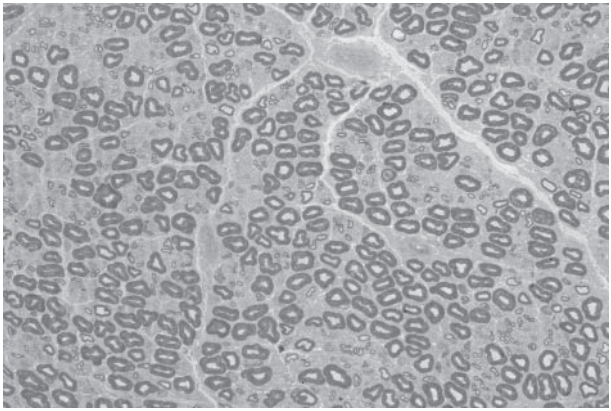

Figure 4.9 Normal nerve with both thickly myelinating, thinly myelinated, and unmyelinated fibers.

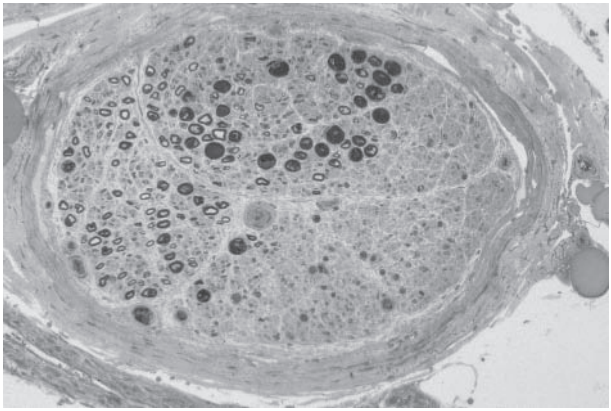

Figure 4.10 Nerve undergoing axonal loss. Nerve fibers of all types are damaged or lost.

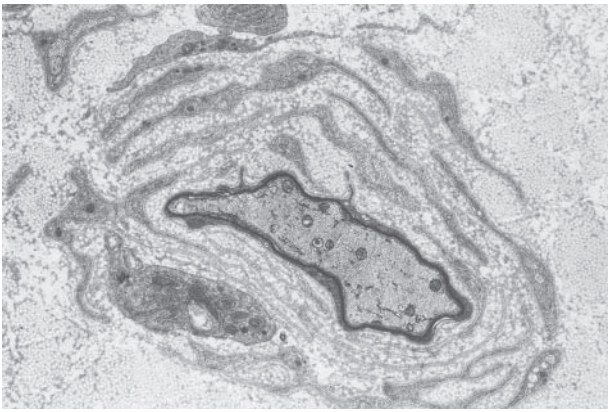

Figure 4.11 Electron microscopy of hypomyelinating hereditary neuropathy, showing classic "onion bulb" formation.

Chapter 5

Stroke and other vascular disorders

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Ischemic stroke

- Ischemic stroke is responsible for 80% of all stroke, with intracerebral hemorrhage responsible for ~15% and subarachnoid hemorrhage for ~5%.
- Transient ischemic attack (TIA)
  - Classical definition: symptoms and signs resolve within 24 hours. Likely outdated as MRI shows evidence of permanent infarction in many cases of "classical" TIA.
  - New tissue-based definition: proposed by American Heart Association in 2009 defines TIA as transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction
- Early risk of stroke after TIA is high:
  - 90-day risk, 3%–17.3%
  - Risk or recurrence is highest in first 48 hours, so rapid evaluation is warranted.

Etiology

- Atherothromboembolism:
  - Carotid and vertebral stenosis
  - Intracranial stenosis
  - Aortic arch atheroma
- Cardioembolism
- Small vessel disease (lacunar stroke), typically related to history of hypertension or diabetes
- Arterial dissection
- Inflammatory vascular disorders:
  - Giant cell arteritis
  - Systemic vasculitides, e.g., SLE
  - Primary angiitis
- Hematological disorders:
  - Antiphospholipid syndrome
  - Thrombophilic states
- Genetic disorders:
  - CADASIL
  - Mitochondrial disorders, e.g., MELAS
  - Sickle cell disease
- Infections:
  - Meningitis, e.g., TB
  - HIV
- Others:
  - Migraine
  - Oral contraceptive, pregnancy

Risk factors

Nonmodifiable

- Age
- Race/ethnicity
- Family history

Modifiable

- Hypertension (most important risk factor for both ischemic and hemorrhagic stroke)
- Smoking
- Diabetes
- Obesity
- Atrial fibrillation
- Prior TIA
- Coronary heart disease
- Physical inactivity

Clinical features

Anterior circulation (carotid territory)

- Amaurosis fugax/retinal infarction
- Hemiparesis
- Hemisensory loss
- Hemianopia (optic tract and radiation)
- Dysphasia
- Sensory inattention
- Visual inattention

Posterior circulation (vertebrobasilar)

- Ataxia
- Cranial nerve involvement:
  - Diplopia
  - Facial sensory loss
  - LMN facial palsy
  - Vertigo
  - Dysphagia
  - Dysarthria
- Hemiparesis (may be bilateral)
- Hemisensory loss (may be bilateral)
- Hemianopia (occipital lobe)
- Cortical blindness—basilar artery occlusion

Lacunar strokes

- Pure motor strokes (face, arm, and leg) in the posterior limb of internal capsule or in pons
- Pure sensory stroke (thalamus)
- Ataxic hemiparesis (weakness and ataxia affecting the same side) due to a pontine or internal capsule lesion
- Clumsy hand/dysarthria due to a pontine or internal capsule lesion
- Typically due to small vessel disease from hypertension or diabetes, though identical clinical syndrome can occur with embolic infarct or hemorrhage

Investigations

Blood tests (first-line)

- CBC
- Ca^{2+} (hypo- or hypercalcaemia may be a cause of focal deficit)
- Electrolytes, creatine, LFT
- Glucose
- Cholesterol
- Clotting screen

Blood tests (second-line, consider in select cases)

- ESR
- Thrombophilia screen (though treatment implications are unclear):
  - Protein C, S, and antithrombin III defects;
  - Factor V Leiden mutation 20210GA
  - Antiphospholipid antibody
  - Lupus anticoagulant
- Blood cultures (endocarditis)
- Homocysteine (though not clear that vitamin supplementation reduces recurrent stroke)
- Lactate
- Cardiac enzymes
- Thyroid function

Other investigations

- Urine analysis (diabetes, hematuria in bacterial endocarditis or vasculitis, toxicology screen)
- ECG (AF, MI)
  - Consider longer cardiac monitoring to screen for paroxysmal AF
- Surface echocardiogram or transesophageal echocardiogram.

Imaging

See next section for details.

Imaging of ischemic stroke

Brain imaging

CT scan (Figs. 5.1 and 5.2)

- CT should be performed as soon as possible especially if thrombolysis is being considered.
- May detect other unexpected lesions, e.g., tumors
- Contrast not indicated and can be misleading
- A normal scan excludes hemorrhage but not infarct.
- Small hemorrhages lose their high density (white), become iso- then hypodense and therefore may be indistinguishable from infarct: in small hemorrhages by 7–10 days, larger hemorrhages 2–3 weeks.
- Small infarcts less likely to be visible than large ones. 90% of large infarcts are visible at 48 hours compared to 40% of lacunar or small cortical infarcts.

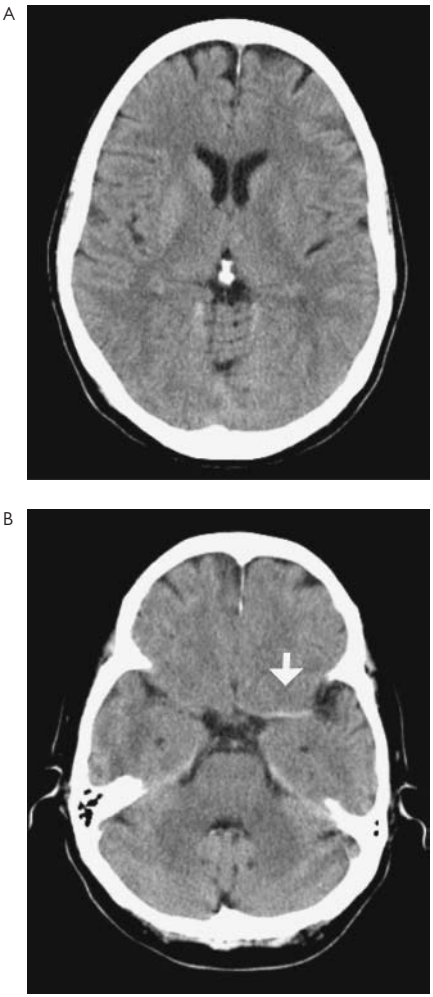

Figure 5.1 CT of acute stroke. Acute left MCA territory infarct. (A–D) Nonenhanced CT images of head obtained within 1 hour of a patient with acute onset of facial droop and right-sided weakness. (A) Axial image at the level of the basal ganglia shows slight loss of gray-white distinction along the left insular lobe and left putamen consistent with acute ischemia. (B) Axial image shows a dense MCA sign (white arrow) consistent with acute thrombus in the vessel.

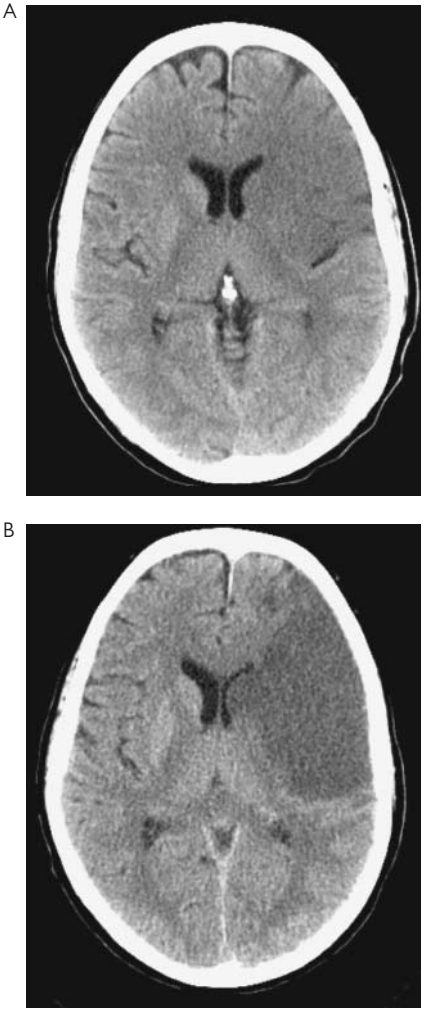

Figure 5.2 CT of evolving acute stroke. Axial CT image at the level of the basal ganglia in the same patient obtained within 7 hours (A) and 24 hours (B) after the onset of symptoms. Progression of low attenuation is seen within the left frontal and insular lobes and involving the deep gray and white matter structures.

- Large infarcts may show subtle changes by 6 hours—depends on expertise of interpretation. Between 10 days and 3 weeks infarcts become isodense and difficult to define.
- After 2–3 months they are more visible, showing same density as CSF.

MRI (Fig. 5.3)

- May be an option for initial imaging of stroke *in select centers*
- Shows ischemic lesion more often than CT and therefore useful in those with CT scan negative infarcts
- Diffusion-weighted imaging (DWI) shows changes within minutes. Useful to distinguish acute from chronic changes. More sensitive but not specific for infarction. Encephalitis, demyelinating plaques, tumors may all show increased signal.
- DWI most useful in identifying minor cortical or lacunar strokes or, in patients with a previous stroke and deteriorating signs, it may show the development of a new lesion.
- True restricted diffusion is verified with corresponding dark signal on apparent diffusion coefficient (ADC) maps. In contrast, high signal on the ADC maps is marker for T2 shine through (artifact) on the diffusion images.
- Multiple infarcts in different vascular distributions suggest cardioembolism or vasculitis.
- T2-weighted images show lesions in 90% by 24 hours.
- However, due to infarct evolution, with routine MR imaging (T2 and T1) "fogging" also occurs and may not show lesions.
- FLAIR (fluid-attenuated inversion recovery) sequences increase sensitivity but will reveal additional incidental lesions, making interpretation more difficult.
- Routine MR sequences will show features for hemorrhage (low T2 signal due to hemosiderin) in 90% indefinitely.
- Gradient echo (GE) or $T2^*$ sequences are the most sensitive for detection of hemorrhage.
- Use of mismatch between perfusion and DWI, which may identify salvageable territory amenable to intervention, is under investigation.

Imaging of vessels

- Imaging of extracranial vessels should be performed in all patients with TIA or mild to moderate stroke affecting carotid circulation.
- Imaging of intracranial and extracranial vessels can be considered for all stroke patients to help define mechanism of stroke and for risk stratification. However, specific management strategy for intracranial or vertebrobasilar stenosis remains unclear at this time.

Doppler US is the simplest and safest method of assessing carotid and vertebral arteries to detect stenosis or dissection. Very operator dependent, and it only images a portion of extracranial vessels.

MRA

- Good correlation between normal MRA and absence of disease
- However, MRA tends to overestimate degree of stenosis since narrowing may be due to stenosis slow flow or turbulence.

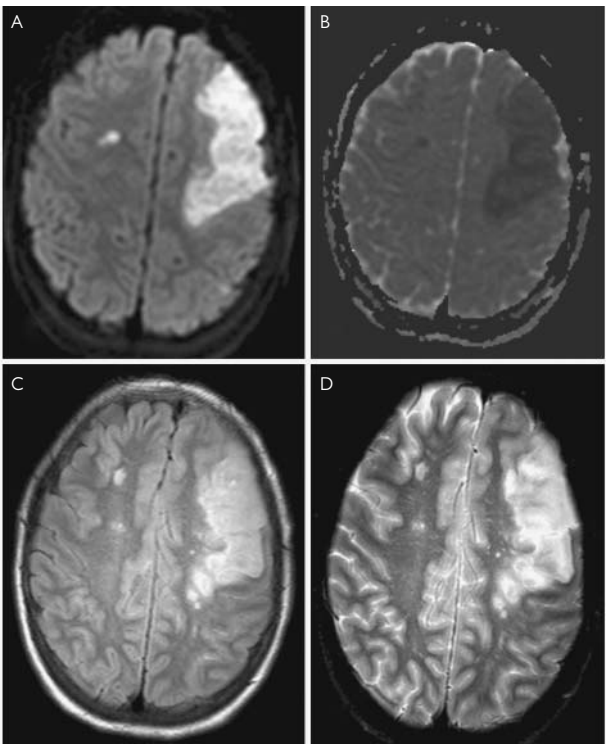

Figure 5.3 Acute left MCA stroke on MRI. (A) DWI axial, (B) ADC map, (C) axial FLAIR, and (D) axial T2-weighted images at corresponding levels. Large area of hyperintense FLAIR and T2 signal region in the left frontal lobe is consistent with branch occlusion of the left middle cerebral artery. Hyperintense diffusion signal, which is hypointense on ADC-weighted images, confirms true restricted diffusion. Note the contralateral right frontal acute infarction as well, which suggests a cardioembolic source.

- Contrast-enhanced MRA gives better morphological assessment but may not differentiate between occlusion and very slow flow ("flow gap").

CT angiography

- Noninvasive option, rapid image acquisition
- May be better than MRA at distinguishing occlusion from slow flow (Fig. 5.4).

A

B

Figure 5.4 Critical stenosis of internal carotid artery. CT angiography demonstrates a tight stenosis at the origin of the ICA on the 2D (A) and 3D (B) reformatted images.

Digital subtraction angiography (DSA or conventional catheter angiography) is the gold standard and will identify stenosis severity including complete occlusions and almost occluded vessels. However, risk of stroke is about 1%. Note: methods of calculation of % stenosis vary.

Arterial dissection

- Contrast-enhanced CT scan is rarely diagnostic.
- MRI with fat-suppressed T1W axials recommended as first choice (Fig. 5.5), though CTA an option as well.
  - "Fried egg appearance"—eccentrically located narrowed lumen within an expanded artery
  - Lumen may be patent (flow void), reduced flow (isointense), or occluded/very slow flow (hyperintense).
  - Surrounding crescent of intramural hematoma (hyperintense on TW1 axials with fat suppression)
  - Absence of high signal in lumen on GE (T2*) indicates occlusion.
- Doppler ultrasound may demonstrate intimal flap, a double lumen, and intramural thrombosis.
- If MRI not diagnostic, CTA or MRA may show lesions.
- DSA remains the gold standard.

A

Figure 5.5 MRA of carotid artery dissection. (A) Source image from a three-dimensional time of flight axial MRA demonstrates the true and false lumens of the extracranial left internal carotid artery (white arrow).

B

Figure 5.5 (*Contd.*) MRA of carotid artery dissection. (B) MIP coronal view of the circle of Willis demonstrates signal in both lumens of the visualized extracranial carotid artery (white arrow). The brighter intensity in both images demonstrates the true lumen.

Management of ischemic stroke

General management

- Admission to a stroke unit has been shown to reduce mortality by 30% and improve outcome.
- Blood pressure: cerebral autoregulation is disturbed after stroke.
  - Optimal management uncertain. Routine BP lowering is not recommended.
  - May consider treatment (goal ~15% reduction) if sustained BP >220/120. Lower levels in the acute stage should not be treated unless coexistent with hypertensive encephalopathy, aortic dissection, acute MI, or LVF.
- Oxygenation: no data available but O_2 should be given if saturation <92%.
- Control of blood glucose: hyperglycemia in acute stroke associated with poor outcome. Maintain normal levels with insulin if necessary.
- Fever should prompt a search for infectious source, and consideration of antipyretics as hyperthermia can exacerbate brain injury.
- Intravenous fluids with isotonic saline to maintain cerebral perfusion.
- Swallowing and nutrition: if abnormal swallow arrange speech-language pathology assessment. Consider NG tube or PEG tube feeding. Advice from dietitian for nutritional support.

- Physiotherapy: early mobilization and rehabilitation to minimize physical deterioration, restore function, and develop strategies for coping with impairment.
- DVT prevention: avoid dehydration. Compression stockings. Consider use of thromboprophylaxis if prolonged immobilization with SC heparin.
- Seizures occur in 2%—focal or generalized. Conventional AED for recurrent events.
- Monitor for post-stroke depression and neuropsychiatric complications such as emotional lability, which occurs in 50%.

Specific treatment of acute stroke

Acute ischemic stroke

- Intravenous (IV) thrombolysis:
  - Intravenous recombinant tissue plasminogen activator (rtPA) given within 3 hours improved functional outcome (NINDS trial). Most benefit obtained if given within first 90 minutes.
  - ECASS-3 trial also showed a benefit to IV rtPA in the 3–4.5 hour window; though there were slight differences in exclusion criteria compared with the NINDS 0–3 hour trial
  - Defining an accurate time of symptom onset (or "last time known to be normal") often requires diligent history taking.
  - Thombolytic candidates must have BP <185/110 before treatment and maintained <180/105 after thrombolytic treatment.
  - Major complication is hemorrhagic transformation (occurs in ~6% with no overall increase in mortality).
  - Organized stroke systems of care should be used to facilitate rapid evaluation and treatment of potential thrombolytic candidates
  - Avoid antiplatelets and anticoagulants for 24 hours after rtPA. Monitor patients closely after treatment for neurological deterioration and BP.
- Intra-arterial (IA) thrombolysis
  - Limited randomized trial data to support its use
  - Endovascular treatment with thrombolytic agents or mechanical clot removal devices may be an option for individuals with large vessel occlusions (carotid, proximal MCA, or basilar).
  - May be a longer time window than IV thrombolysis
  - Combined IV-IA approaches are also under investigation.
  - Individuals who are otherwise good candidates for IV thrombolysis should NOT be offered IA treatment, as time to treatment is a key factor.
- Antiplatelet drugs:
  - Aspirin started within 48 hours reduces mortality and recurrent stroke.
  - CT first to exclude hemorrhage
- Anticoagulation:
  - Routine anticoagulation of stroke patient is *not* recommended. No evidence that early anticoagulation reduces morbidity, mortality, or early recurrent stroke. Studies have shown that immediate treatment with heparin reduces DVT and PE but associated with increased risk of cerebral hemorrhage.

  - AF or other cardioembolic cause, treat with aspirin and start oral anticoagulation after approximately 2 weeks, though no data on safety regarding when to start anticoagulation.
  - At present no data on heparin in dissection, though both anticoagulation and antiplatelet therapy for 3–6 months are considered treatment options for dissection.
- Surgery: hemicraniectomy may be considered in raised intracranial pressure (malignant MCA occlusion), and it has been shown to be beneficial in reducing mortality in clinical trials. Posterior fossa craniectomy considered for large cerebellar infarcts.

Prevention of ischemic stroke

Primary prevention

Atheroembolism

- Avoidance and treatment of risk factors:
  - Hypertension
  - Diabetes
  - Smoking
  - Hypercholesterolemia
- The risk of stroke in patients with asymptomatic carotid stenosis is much less than in those with symptomatic stenosis—2% per annum versus 15% in the first year.
- The Asymptomatic Carotid Atheroclerosis Study (ACAS) found a statistically significant reduction in stroke risk after surgery for stenosis, at least 60%.
  - Benefit seen at 5 years, so patients must have 5 year expected life span
  - Consider patient factors, comorbidities

Cardiac embolism

- AF: nonrheumatic AF risk of stroke is five-fold. Risk is higher if other risk factors are present:
  - Increasing age
  - Hypertension
  - Impaired LV function
  - Valve disease
  - Diabetes
- High risk: 8%–12% annual stroke risk if age >75 years, diabetes, hypertension. Warfarin with target INR 2–3 reduces stroke risk by 60%. If warfarin contraindicated, use aspirin.
- Low risk: 1% annual stroke risk. If age < 65 years and no other risk factors, use aspirin.

Secondary prevention

- Lifestyle changes, e.g., smoking, weight, and alcohol reduction
- BP: Hypertension is perhaps the most important risk factor to control post-stroke.
  - PROGRESS trial showed reduction in recurrent hemorrhagic and ischemic stroke using perindopril and indapamide even if BP normal.

- Antiplatelet drugs:
  - Aspirin (75–300 mg) reduces the risk of recurrent stroke and vascular death by 18%.
  - Combination of aspirin + dypiridamole (200 mg) may be more effective than aspirin alone.
  - Clopidogrel (75 mg) may be slightly more effective and should be used in those intolerant of aspirin.
  - Combination of aspirin plus clopidogrel does not offer benefit in secondary stroke prevention over single antiplatelet and is associated with increase in bleeding complications.
- Cholesterol lowering
  - Lifestyle/dietary changes
  - If stroke/TIA plus coronary disease or symptomatic atheroclerosis, use statin to goal LDL of <100 mg/dL (70 mg/dL if very high risk)
  - Statins should also be used in atherosclerotic stroke/TIA, even in individuals without coronary disease.
- Warfarin has no benefit for secondary stroke prevention for patients in sinus rhythm.
- AF patients should be anticoagulated after stroke.
- Surgical/endovascular treatment:
  - Carotid endarterectomy is highly beneficial in those with >70% stenosis; moderately beneficial for those with 50%–69%.
  - Higher risk of stroke and therefore may be a greater benefit in those with recent symptoms, ulcerated plaque, and hemispheric presentation rather than amaurosis fugax
  - Secondary data analysis of trials indicates greater benefit if surgery done within 2 weeks of symptom onset.
  - Operative mortality, 1.1%; operative risk of stroke, ~5%.
  - Carotid angioplasty and stenting currently being evaluated; may be an option for individuals at high surgical risk, thoug h optimal patient selection remains to be defined by clinical trials.

Cerebral venous thrombosis

Epidemiology

- Incidence 0.22/100,000
- Most frequent in neonates. Women > men
- Risk factors:
  - Pregnancy and puerperium
  - Oral contraceptive pill
  - ENT infections
  - Cancer
  - Prothrombotic states
  - Dural AV fistulae

Clinical features

- ICP as idiopathic intracranial hypertension:
  - Headache

  - Visual obscurations
  - Papilledema
  - VIth nerve palsy
- Focal neurological deficit:
  - Hemiparesis
  - Dysphasia
  - Seizures
- Diffuse encephalopathy:
  - Delirium
  - Coma
  - Seizures
  - Multifocal neurological deficits
- Cavernous sinus syndrome
  - III, IV, VI, V^1 palsy
  - Proptosis

Investigations

- Imaging (see below)
- Consider screen for prothombotic states

Management

- Treat associated infection.
- Anticoagulation with heparin followed by warfarin for 6 months. Consider lifelong if prothrombotic conditions exist.
- If not responding or deteriorating, consider local thrombolysis therapy.
- ICP:
  - Repeated LP or external lumbar drain or lumbo-peritoneal shunt
  - Mannitol
  - If not responding or deteriorating, consider sedation, ventilation, and decompression craniectomy.
- Seizures: treat with appropriate antiepileptics.

Imaging in venous thrombosis

Difficult diagnosis to make clinically and radiologically.

- CT scan (Fig. 5.6) reveals:
  - Local or diffuse swelling
  - Hyperintense venous sinuses and cortical veins
  - Parenchymal lesions—often multiple, low attenuation lesions with edema and hemorrhage (high density). Thalami and basal ganglia involved if internal cerebral veins thrombosed. SAH may be present.
- Contrast-enhanced CT: enhancement of dural sinuses around nonenhancing expanded thrombus ("delta sign")
- CT venogram demonstrates filling defects and expansion of thrombosed sinuses.
- MRI shows (Fig. 5.7):
  - Acute: absent flow void in dural sinus (isointense on T1W but hypointense on T2W (mistaken for flow void). Subacute: sinus hyperintense on T1W and T2W.
  - Parenchymal lesions are hyperintense on T2W/FLAIR with edema ± hemorrhage ± enhancement ± swelling local or diffuse.

Figure 5.6 CT of venous sinus thrombosis. Axial images of a noncontrast head CT demonstrates high attenuation within the superior sagittal sinus (arrow in A and B), cortical vein (A) and left transverse sinus (arrow in C) consistent with hyperdense clot.

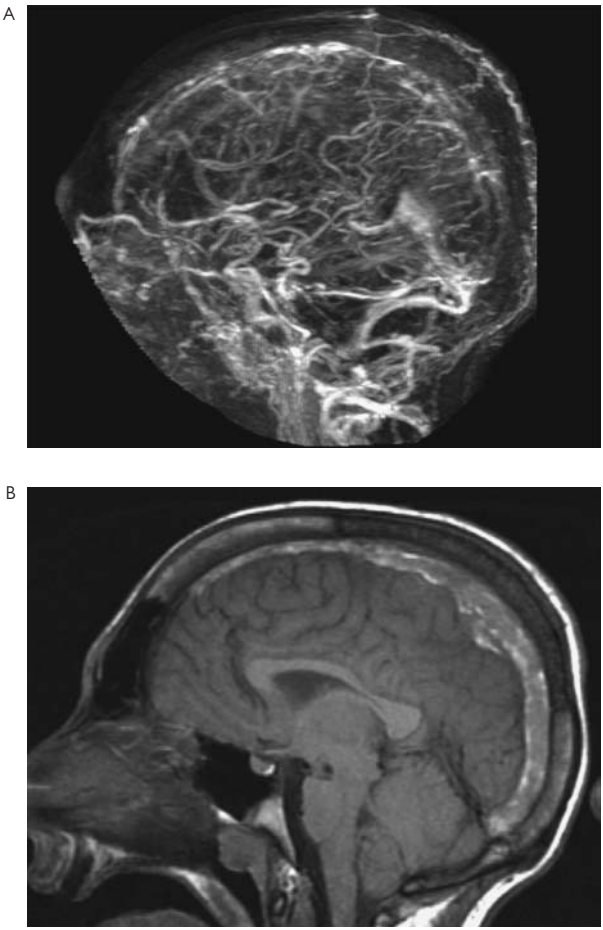

Figure 5.7 MRV and MRI of venous sinus thrombosis. Sagittal MIP view of a contrast enhanced MRV (A) demonstrates lack of signal along the superior sagittal sinus. Correspondingly, diffuse hyperintense clot is seen on the sagittal T1-weighted image (B).

- MRV shows loss of flow, or irregularity or severe narrowing indicating thrombus.
- Some cases may require DSA for further evaluation.
- Multiple modalities may be required to make a diagnosis.
  - Prominence of edema prior to and around hemorrhages suggests venous hypertension.
  - Degree of normal variation in size of lateral sinuses and cortical veins makes interpretation difficult.

Primary angiitis of the central nervous system (PACNS)

Clinical features

- Rare disorder
- Typically a subacute progressive encephalopathy, with headache. May be punctuated by seizure, or stroke, though presentation with only isolated stroke is unusual
- Can affect brain or spinal cord
- Classically progressed to severe disability or death in the pre-immunosuppressive era

Differential diagnosis (partial list)

- CNS lymphoma, intravascular lymphoma
- Multiple sclerosis
- Multiple cardioembolic strokes
- Chronic progressive noninflammatory vasculopathy (moya moya)
- Reversible cerebral vasoconstriction syndromes (RCVS, see later)
- Systemic inflammatory conditions (Sarcoid, Bechets, Susac, etc.)
- Infectious etiologies (TB, Lyme, syphilis, Herpes zoster, fungal meningitis)

Imaging

- Brain MRI findings are nonspecific (Fig. 5.8) with periventricular, subcortical white matter hyperintensities with or without evidence of cortical infarcts and hemorrhagic foci.
- Catheter angiography may be normal or may show multiple luminal irregularities, narrowings, occlusions, and sometimes aneurysms. Vascular narrowings are not necessarily specific for vasculitis and can be seen in other conditions such as atherosclerosis.

Investigations

- Serum tests to screen for systemic inflammatory conditions and associated systemic vasculitis, though systemic inflammatory markers may be normal.
- Echocardiography to rule out cardioembolism
- CSF frequently shows elevated protein or lymphocytic pleiocytosis, though normal CSF does not exclude PACNS.

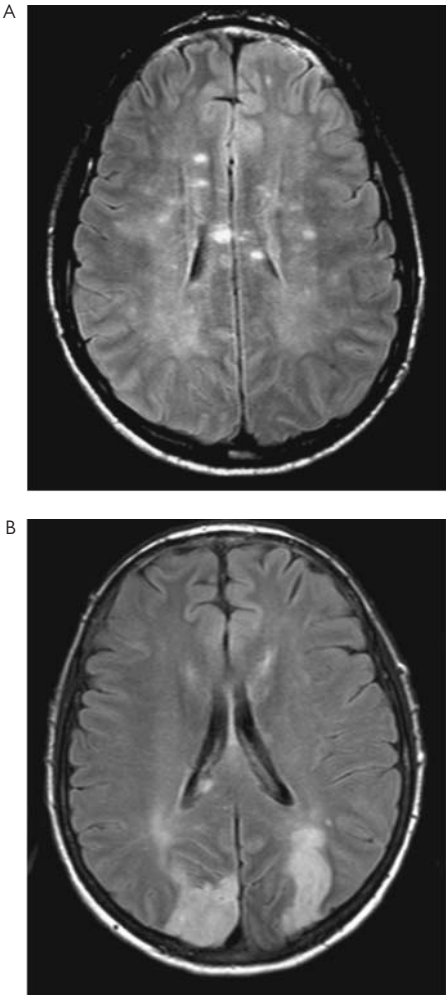

Figure 5.8 CNS vasculitis. Axial FLAIR weighted images at two different levels show nonspecific hyperintense foci throughout the deep white matter where large geographic hyperintense areas in the biparietal cortical gray matter subcortical and deep white matter. Differential diagnosis is extensive but these findings can be compatible with vasculitis, which was confirmed clinically in this patient.

- Brain and meningeal biopsy should be performed to confirm diagnosis, given the significant toxicities of treatment, and the potential to discover alternative diagnoses at biopsy.
- Biopsy may also be negative given potential for patchy involvement, which makes diagnosis particularly challenging.

Management

- First-line treatment is typically with steroids in combination with cyclophosphamide. Must monitor for treatment complications.
- Typically treat for at least 1–2 years.

Reversible cerebral vascoconstriction syndromes (RCVS)

- Also described as Call-Fleming syndrome, benign angiopathy of the central nervous system (BACNS), postpartum angiopathy, drug-induced arteritis (cocaine, methamphetamine).
- Important to distinguish from PACNS, which requires long-term aggressive immunosuppressive treatment, whereas RCVS do not.
- More common in women than men. Classic presentation is with acute onset severe ("thunderclap") headache, which can mimic subarachnoid hemorrhage/aneurysm rupture. Critical to exclude SAH with CSF studies.
- May present without focal features or may have symptoms of stroke or seizure.
- CSF should be normal or near normal in RCVS. If abnormal, consider other etiologies.
- Brain MRI may be normal or may show areas of infarction.
- Intracranial vessel imaging with MRA, CTA, or catheter angiography shows multifocal segmental arterial vasoconstriction. Vasoconstriction reverses within days to weeks (typically less than 12 weeks).
- Management options include short-term course of oral steroids, calcium channel blockers, or simply observation, since some patients may resolve spontaneously without treatment.

Spontaneous intracerebral hemorrhage (ICH)

- Spontaneous ICH is a common cause of morbidity.
- Twenty percent of strokes caused by cerebral hemorrhage (75% ICH and 25% SAH).
- Risk factors for ICH are similar to those with ischemic stroke:
  - Age
  - Male gender
  - Hypertension
  - Smoking
  - Diabetes
  - Excessive alcohol use

Etiology

- Hemorrhage is due to rupture of small vessels and microaneurysms in perforating vessels.
- Underlying vascular conditions should be considered:
  - AVM
  - Aneurysm
  - Cavernoma
  - Amyloid angiopathy
  - Dural arteriovenous fistula
  - Cerebral venous thrombosis
- Hemostatic factors:
  - Anticoagulant drugs
  - Anti-platelet drugs
  - Coagulation disorders
  - Thrombolytic therapy
- Other etiologies:
  - Drug abuse (cocaine)
  - Moya moya syndrome
  - Hemorrhage into a tumor (metastatic malignant melanoma, renal, thyroid, and lung carcinoma, choriocarcinoma, oligodendroglioma, and ependymoma)
- Clues to the etiology may come from site:
  - Basal ganglia in hypertensive bleeds
  - Sylvian fissure in MCA aneurysms
  - Lobar bleeds in amyloid angiopathy, though hypertension is also an important risk for lobar bleeds.

Clinical features

- Sudden ictus as a stroke
- ± Signs and symptoms of increased ICP—severe headache and vomiting
- Seizures and meningism

Management

- Standard medical support and rehabilitation evaluations as in ischemic stroke
- Surgical evacuation of the hematoma depends on location, age, and premorbid performance status of the patient. Recent STICH trial suggests no benefit to routine early hematoma evacuation.
- Infratentorial hematomas are special cases—may warrant surgical intervention for evacuation or shunt insertion for hydrocephalus.
- Stop anticoagulants and antiplatelet drugs.
- Sequential compression devices for DVT prophylaxis; may consider subcutaneous heparin after 3–4 days if persistent hemiplegia *and* documentation of cessation of hemorrhage.
- Correct coagulation deficits, though optimal method of correction is unknown.
- Monitor for seizures, low threshold to consider antieplipetics, particularly for lobar ICH

- Blood pressure management:
  - Ongoing trials hope to address the role of acute blood pressure lowering in ICH
  - Need to balance potential risk of elevated BP contributing to hematoma expansion with risk of cerebral hypoperfusion if BP lowered too much
  - Until trials are complete, it is probably reasonable to consider modest (e.g., 10%–15%) BP reduction if SBP >180 or MAP >130. Consider ICP monitoring if suspicion of elevated ICP to maintain cerebral perfusion pressure >60–80 mmHg.

Imaging of ICH

Guidelines

Nonenhanced CT (Fig. 5.9) and then:

1. If hematoma location and history typical of hypertension, i.e., striatocapsular (65%), thalamus (20%), pons and cerebellum (10%), no further imaging necessary.
2. If atypical history or unusual CT appearance, contrast-enhanced MRI; T2* may give evidence of previous hemorrhagic lesions. Also consider MRV or CT venography.
3. If there is suspicion of an underlying vascular abnormality or an aneurysm, perform a DSA.
4. If initial investigations are unhelpful, consider repeat delayed MRI or DSA, as the hematoma can obscure potentially relevant findings in the acute phase.

Serial imaging features

Hyperacute (<6 hours)

- Presence of oxyhemoglobin, mass effect, and edema
- CT: isodense with low-density elements ("swirl")
- MRI: T1W isointense, T2W hyperintense, T2* heterogeneous or hypointense

Acute (6 hours to 3 days)

- Presence of deoxyhemoglobin, mass effect, and edema
- CT: hyperdense
- MRI: T1W isointense, T2W hypointense, T2* hypointense

Early subacute (3 days to 1 week)

- Presence of cellular methemoglobin, mass effect, and edema
- CT: hyperdense
- MRI: T1W hyperintense, T2W hypointense, T2* hypointense

Late subacute (1 week to 1 month)

- Free methemoglobin, minimal mass effect, and edema
- CT: isodense with hypodense rim
- MRI: T1W hyperintense, T2W hyperintense, T2* hypointense

Figure 5.9 CT of acute hypertensive ICH. Large acute hemorrhage centered in the right lentiform nucleus with marked surrounding mass effect, leftward midline shift, and intraventricular extension of bleeding.

Chronic (months)

- Presence of hemosiderin. No mass effect or edema
- CT: hypodense
- MRI: T1W, T2W, and T2* hypodense

Note: Coagulopathy and severe anemia result in isodense acute hematoma on CT. Rapidly accumulating hematomas may have fluid levels.

Subarachnoid hemorrhage (SAH)

Clinical presentation

Clinical severity varies widely.

- Headache—worst-ever headache; "hit on the back of the head." May occur during strenuous activity such as sexual intercourse. Associated with vomiting
- Coma
- Sudden death

Examination may reveal:

- Typical signs of meningism (neck stiffness, photophobia, positive Kernig sign);
- Presence of subhyaloid hemorrhages on fundoscopy
- Signs of ICP (bradycardia, hypertension);
- (Late) papilledema

See Tables 5.1–5.3 for grading systems for SAH.

Causes

- Berry aneurysm
- Trauma
- Traumatic and infectious aneurysms
- Clotting disorder or anticoagulant, e.g., warfarin
- Dural AVM

Diagnosis

1. CT scan positive in 95% in first 24 hours. If negative proceed to:
2. LP: measure opening pressure and look for evidence of blood and/or xanthochromia.
3. Check clotting screen.
4. If CT scan is positive or LP positive, → CT angiogram or digital subtraction angiography (formal catheter angiogram).

Management

Cerebral vasospasm

- Focal cerebral ischemia as a result of cerebral artery vasospasm is the biggest cause of neurological morbidity.
- Vasospasm is maximal from 5–10 days post-SAH.

Standard prevention and treatment

- Calcium antagonist nimodipine 60 mg every 4 hours has been shown to decrease the rate of development of vasospasm-induced ischemic deficits from over 25% to <20%.
- Hydration with normal saline
- "Triple H" therapy = hypertension (with inotropic drugs), hemodilution, and hypervolemia and is used in established vasospasm
- Use of colloidal solutions such as albumin, dextran, or hexastarch (to improve flow and rheology viscosity)

Table 5.1 Hunt and Hess Scale for SAH

Grade	Blood on CT
1	Asymptomatic, mild headache, slight nuchal rigidity
2	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3	Drowsiness/confusion, mild focal neurologic deficit
4	Stupor, moderate–severe hemiparesis
5	Coma, decerebrate posturing

Hunt WE, Hess RM (1968). Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *Journal of Neurosurgery* **28**(1):14–20.

Table 5.2 World Federation of Neurological Surgeons (WFNS) grading system for SAH

Grade	Glasgow Coma Scale (GCS) score	Motor deficit
1	15	Absent
2	13–14	Absent
3	13–14	Present
4	7–12	Present or absent
5	3–6	Present or absent

Table 5.3 Fisher classification of SAH on the basis of the blood load on the brain CT scan

Grade	Blood on CT
1	No blood detected (SAH diagnosed on LP)
2	Diffuse/vertical layers <1 mm thick
3	Localized clot or layers >1 mm thick
4	Intra cerebral or intraventricular clot with diffuse or no SAH

Fisher CM, Kistler JP, Davis JM (1980). Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery* **6**(1):1–9.

- Chemical (papaverine) or balloon angioplasties to physically open the cerebral arteries are also used but with mixed results. Appears most useful around the time of endovascular (coil) or neurosurgical (clip) interventions, but the effects are probably not sustained.

Investigations

- Many centers utilize transcranial Doppler to monitor cerebral arterial flow as a surrogate marker of vasospasm.
- Diffusion/perfusion MRI scans are also used when available to study deficits in regional cerebral perfusion.

Securing the aneurysm to prevent rebleeding

Timing of the definitive treatment of cerebral aneurysms (coiling or clipping) will depend on:

- Patient's general and neurological condition
- Extent of angiographically defined vasospasm
- The ethos of the neurosurgical unit as to what degree the patients are treated "early" or "late"
- However, only in those with large ICHs secondary to middle cerebral artery aneurysms is emergency treatment advocated.

Hydrocephalus See "Hydrocephalus," p. 376.

Outcome and prognosis

- Angiogram-negative SAH. Following SAH, cerebral angiography is negative in 15%–20% of cases.
  - Consider delayed repeat angiogram to verify absence of aneurysm.
  - Perimesencephalic SAH is angiogram negative and typically has a benign course. Patient may have headaches for several weeks but with no further hemorrhages. Small risk for development of hydrocephalus
- Patients with SAH due to an aneurysm:
  - Approximately one-third die, usually out of hospital.
  - Approximately one-third recover completely.
  - Approximately one-third recover with some disability.

Imaging of SAH

Diagnosis of SAH

- Nonenhanced CT positive in 95% within the first 24 hours. Sensitivity decreases with time so that at 1 week <50% positive (Fig. 5.10).

Imaging features

- Blood (high density) in subarachnoid space ± intraparenchymal ± subdural space
- Distribution of blood may indicate site of aneurysm:
  - Predominant Sylvian fissure ± temporal lobe = MCA
  - Symmetric distribution or marked involvement of anteroinferior interhemispheric fissure or medial frontal lobe = ACom artery

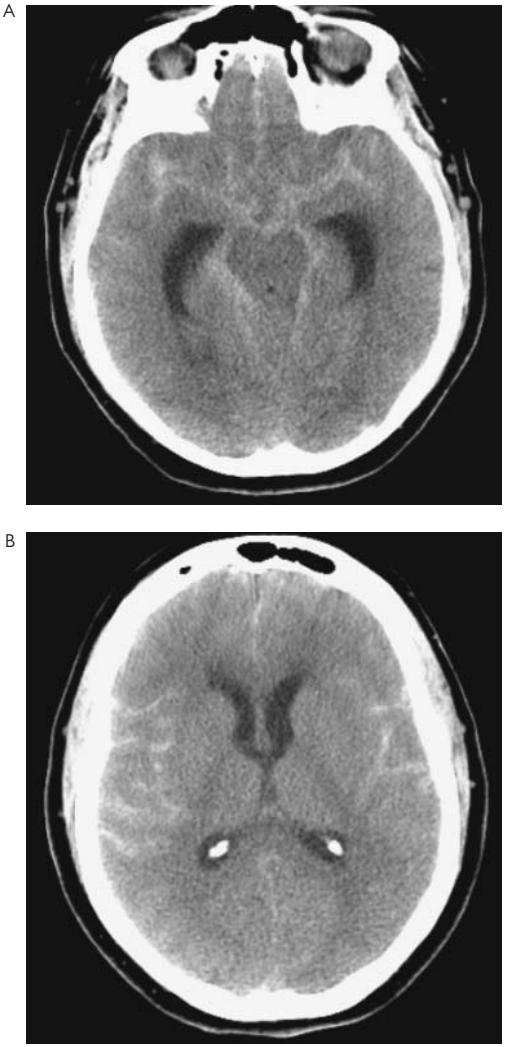

Figure 5.10 CT of acute SAH. Acute subarachnoid hemorrhage with acute hyperdense blood is noted within the basal cisterns and Sylvian fissures. Note the mild degree of communicating hydrocephalus.

  - Lateralization in suprasellar, prepontine, ambient cisterns ± tentorial subdural component = PCom artery
  - Prepontine and 4th ventricle = PIC artery
  - Interhemispheric subdural = pericallosal artery
  - Perimesencephalic hemorrhage, i.e., blood in prepontine, interpeduncular, and ambient cisterns, = venous etiology
- Early communicating hydrocephalus is typical.
- Low attenuation areas may indicate ischemia from vasospasm.

MRI T1W and T2W are relatively insensitive; FLAIR is the best sequence with hyperintensity in the subarachnoid space. Hypointense on T2*.

Differential diagnosis

- Leptomeningeal infection
- Inflammation
- Infiltration
- Propofol anesthetic

Investigation of cause of SAH

- MRA and CTA detect aneurysms >3 mm.
- Negative in 15%–20% of cases of aneurysmal SAH
- Aneurysms are multiple in 20%, and these modalities should provide information on which is responsible as well as vasospasm.
- Phase-contrast MRA removes effect of T1 shortening of blood.

DSA remains the gold standard.

- Greater sensitivity for aneurysms <3 mm
- Largest aneurysm with irregular contour ("nipple") will typically be responsible for the SAH.
- DSA identifies vasospasm accurately.
- However, it is negative in 7%–10%.

Guidelines for imaging for SAH

- If nonenhanced CT positive, then CTA or DSA
- If CTA positive, then surgery or DSA + endovascular coiling
- If CTA negative, then DSA
- If DSA positive, then surgery or endovascular coiling
- If DSA negative, this may be due to vasospasm or large hematoma. Repeat DSA after an interval of 1 to 2 weeks
- In patients with a classic perimesencephalic pattern on CT in excellent clinical condition and no vasospasm, a second angiogram may not be necessary.

Saccular aneurysms

- These are well-defined extra-axial lobulated lesions that may present as a result of an SAH or size (>2.5 cm).
- On CT, if patent, show up as hyperdense to brain tissue and enhancing with or without intramural calcification. If thrombosed, appears as hyperdense lesion with calcification commonly.

- MRI shows variable signal due to slow or turbulent flow. Fifty percent have flow void. Thrombosed lesions often hyperintense on T1W and hypotense on T2W images.
- Further investigation is with MRA or CTA or DSA.

Differential diagnosis
- Meningioma, especially in suprasellar region
- Macroadenoma/suprasellar mass (especially hyperintense on T1W)
- CP angle AICA or PICA aneurysm
- Third ventricular mass (basilar tip aneurysm)

Note: Differentiating an unruptured aneurysm from a mass, particularly if thrombosed, can be difficult. Aneurysm should always be considered in the differential of a mass in the classic sites.

Cerebral aneurysms

Berry aneurysms

Cerebral (berry) aneurysms are outpouchings of the vessel walls that occur commonly on the branching points of the cerebral arteries around the circle of Willis in the subarachnoid space.

Incidence and epidemiology
- Prevalence at least 1% in adults in the United Kingdom/United States. Increasingly common with age and in females (2 to 1)
- Aneurysms rarely but classically occur in inherited disorders such as polycystic kidney disease, Marfan syndrome, pseudoxanthoma elasticum. In countries of high prevalence e.g., Japan and especially Finland, familial aneurysms are much more common.

Neuroanatomy

Typical aneurysm sites
- Posterior communicating
- Anterior communicating (Fig. 5.11)
- Middle cerebral branch points (Fig. 5.12)
- Cerebral aneurysms are sized as small (<1 cm maximum diameter), large (1–2.5 cm), and giant (>2.5 cm). Seventy percent of cerebral aneurysms are small. Twenty percent of cases have multiple aneurysms.

Natural history Incidental aneurysms have a hemorrhage rate of less than 1% per annum if less than 7 mm in diameter. Larger aneurysms and patients with multiple aneurysms or with a previous SAH have a higher bleed rate. Risk of bleeding is higher in cigarette smokers and hypertensives.

Presentation

Cerebral aneurysms present in a variety of ways.
- SAH
- Incidentally on screening or for unrelated symptoms (e.g., headache)
- Third nerve palsy (usually painful, following rapid expansion of a posterior communicating artery aneurysm)
- Visual failure (with large ophthalmic segment aneurysms)

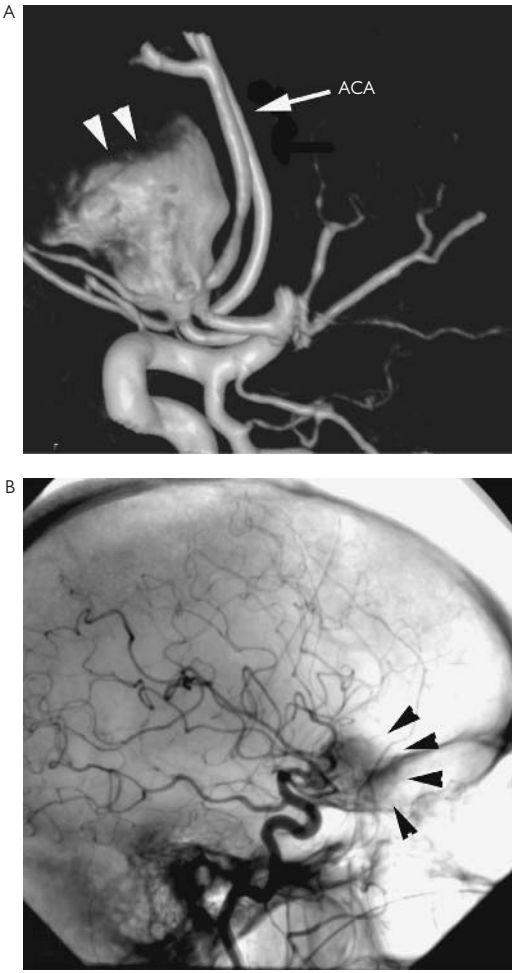

Figure 5.11 Angiogram of anterior communicating artery aneurysm. Sagittal 3D reformatted angiography (A) in the lateral projection demonstrates a partially thrombosed large anterior communicating artery aneurysm. The thrombosed portion is indicated by arrowheads. ACA = anterior cerebral artery. Corresponding lateral view on a digital subtracted image (B) demonstrates the blush of contrast within the aneurysm.

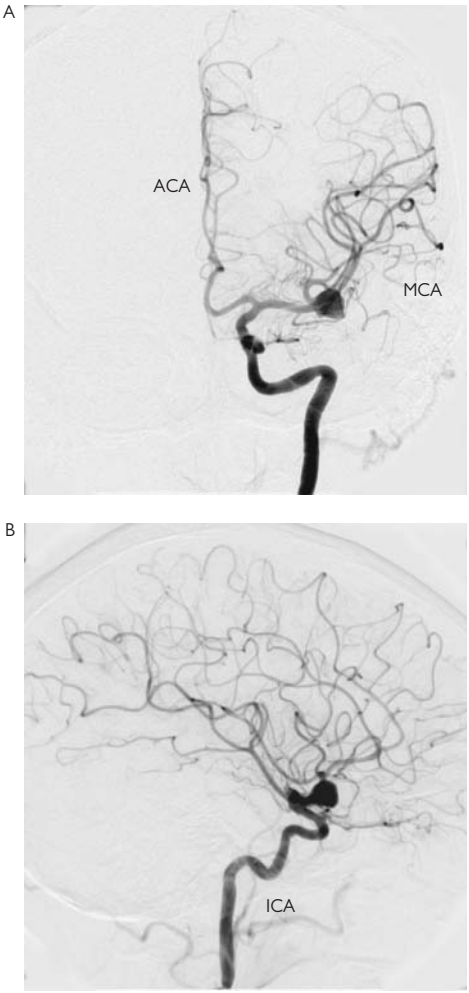

Figure 5.12 Angiogram of middle cerebral artery aneurysm. AP (A) and lateral (B) view of digital subtraction images from a left internal carotid artery (ICA) injection, demonstrating a 1 cm left middle cerebral artery (MCA) bifurcation aneurysm. The anterior cerebral arteries (ACA) are indicated on the AP view.

Treatment

Neurosurgical clipping and neuroradiological coiling are current treatment modalities (Fig. 5.13).

- *Surgical clipping* involves a craniotomy, microdissection of blood vessels of the brain, and passing a titanium clip across the aneurysm neck. May have higher chance of permanent "cure" than with coiling
- *Coiling* has the advantage of obviating the need for a craniotomy. A radiologist passes a catheter endovascularly, similar to performing an angiogram, and then delivers a number of platinum coils into the aneurysm itself. This technique in experienced hands probably has less procedural morbidity than neurosurgical clipping. However, there is a higher incidence of regrowth of the aneurysm and late re-SAH. Therefore, long-term clinical radiological follow-up is advised.

Note: Both techniques need to avoid occluding a cerebral artery or bursting the aneurysm itself. Procedural risk is thus higher in the early period following SAH. Late treatment reduces this risk but increases the risk of re-hemorrhage before treatment, which is highest in the first few days following the initial SAH.

Infectious cerebral aneurysms

Unusual lesions occur most often in the setting of infective endocarditis with septic embolism. These generally occur in the anterior cerebral circulation and are often multiple.

- Pathology: due to acute pyogenic necrosis of arterial wall secondary to vasculitis. Clinically recognized ipsilateral septic thromboembolism precedes hemorrhage in 40% of cases.
- Bacteriology: most frequent causative organisms found in blood culture are Staphylococcus and Streptococcus species.
- Predisposing medical conditions: congenital or acquired cardiac valvular disease, intravenous drug use, and immunocompromised patients.

Investigations

- High degree of suspicion is required in high-risk patients who develop neurological symptoms—CT or MRI imaging.
- Definitive investigation is four-vessel angiography. These lesions will be found most commonly in peripheral branches of the middle cerebral artery; angiography must cover this vascular territory.
- Not uncommon for sequential angiograms to be required to follow the response to antimicrobial treatment if a nonsurgical treatment regimen is instituted.

Management

- Some recommend antimicrobial therapy alone to treat infectious aneurysms, as in up to 50% of cases such lesions resolve or decrease in size following such treatment.
- Timing of any cardiac surgery is crucial to eliminate the infective focus as a further cause for bacteremia and emboli.
- Surgery of infectious intracranial aneurysms is technically difficult, but it may be necessary in selective cases if increase in size or frank abscess.

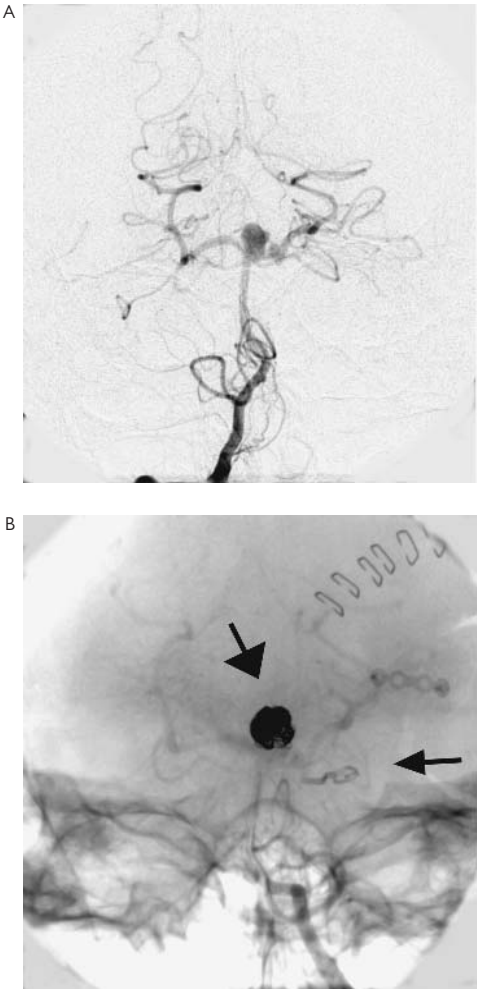

Figure 5.13 Angiogram of basilar tip aneurysm. AP view (A) of a subtracted angiographic image of a vertebral injection demonstrating a dome-shaped basilar tip aneurysm. (B) An unsubtracted image after treatment demonstrates the coil mass in the region of the basilar tip (wide arrow). In addition, a surgical clip from a left posterior communicating artery aneurysm is also seen in this patient (horizontal arrow).

Excision of the lesion with the involved vessel may be required. Neurological deficits may result.

Fungal aneurysms

- Tend to occur more proximally on the intracranial vessels and more frequently involve the large arteries at the base of the brain
- Occur almost exclusively in immunocompromised patients
- *Candida albicans* and *aspergillus fumigatus* are the most common.
- Tend to be more indolent in nature, but their management strategies tend to be similar, i.e., persist with antifungal chemotherapy rather than high-risk surgical/radiological interventions unless absolutely necessary

Traumatic intracranial aneurysms

Unusual condition accounts for <1% of all intracranial aneurysms. Also known as false or pseudo-aneurysms, which define a tear in the arterial wall, associated with extravessel thrombus, which constitutes the aneurysm wall.

Etiologies

- Penetrating injuries such as stab wounds and gun shot wounds
- Following closed head injury: typically and classically at the distal anterior cerebral artery territory, where an artery is torn against the under edge of the falx cerebri. It may also occur at the skull base, where it can cause carotico-cavernous fistulae or occlusion.

Clinical presentation is usually as a delayed cerebral hemorrhage following an otherwise unremarkable recovery from brain injury. A high index of suspicion is required.

Treatment is with neurosurgical excision or with endovascular treatment if ruptured. Optimal treatment of unruptured pseudo-aneurysms is unknown.

Cerebral arteriovenous malformations (AVM)

Incidence

- Ten times less common than cerebral aneurysms
- Rarely multiple except in hereditary hemorrhagic telangiectasia
- Congenital in origin

Pathology

They consist of tangles of pial blood vessels with characteristic early shunting of blood from arteries to veins.

Clinical presentation

- Frequently asymptomatic through life
- May present with ICH, seizures
- Unusual manifestations result from development of a vascular steal or venous hypertension phenomenon.

Natural history studies

Inadequate but risk of hemorrhage is between 2% and 4% per annum. Features associated with risk are as follows:

- Intranidal aneurysms
- Venous stenosis
- Ectasia
- Old age

AVM size is *not* related to hemorrhagic risk.

Diagnosis

- *CT*. Nonenhanced scan may be normal or show an area of hyperdensity with no mass effect. Twenty percent show calcification. With contrast, avid enhancement and a large draining vein may be visualized.
- *MRI*. Mesh of flow voids, large draining veins. Slow-flow lesions may enhance (Fig. 5.14).
- *DSA* (Fig. 5.15). Defines nidus size and architecture accurately. Identifies feeding arteries, the presence of deep or superficial cortical draining veins, flow rate (important for endovascular planning), intranidal aneurysms (in >50%), venous stenosis

Management

- Decisions are critically dependent on angiographic findings of size, shape, position, presence of intra- or extranidal aneurysms, patient age, symptoms, and prior hemorrhage.
- AVMs are relatively benign in the medium term and bleeding risk is probably not altered by partial treatment.
- Symptomatic treatment, e.g., anticonvulsants, and regular follow-up, is an initial option.
- Aim of intervention is complete obliteration. Three treatment options may be used alone or in combination:

Neurosurgery

- Offers the chance of a cure at one operation but is difficult with a significant morbidity
- Larger lesions cause normal pressure perfusion breakthrough.
- Surgical risk can be graded with the Spetzler–Martin grading system between 1 and 5:
  - 1, 2, or 3 points depending on size (<3 cm, 3–6 cm, >6 cm)
  - 1 point if deep venous drainage
  - 1 point if eloquent cortex
- Pre-operative embolization reduces vascularity.
- Significant incidence of residual AVM following surgery
- Small peripheral AVMs with recent hemorrhage ideal surgical targets

Neuroradiological embolization

- The goal is to occlude nidal vessels with either NBCA glue or onyx (liquid embolic agents).
- Only 10%–25% can be obliterated completely.

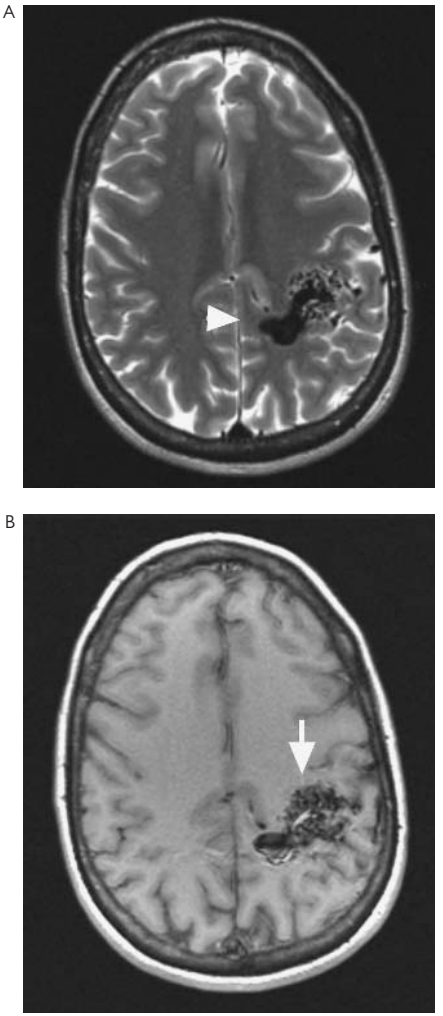

Figure 5.14 MRI of arteriovenous malformation. Axial T2 (A) and T1 postcontrast (B) images demonstrate a nidus of abnormal flow voids (vertical white arrow) consistent with serpiginous collection of vessels, likely arterial, and a large flow void (horizontal arrowhead), demonstrating a large draining vein in the left parietal lobe.

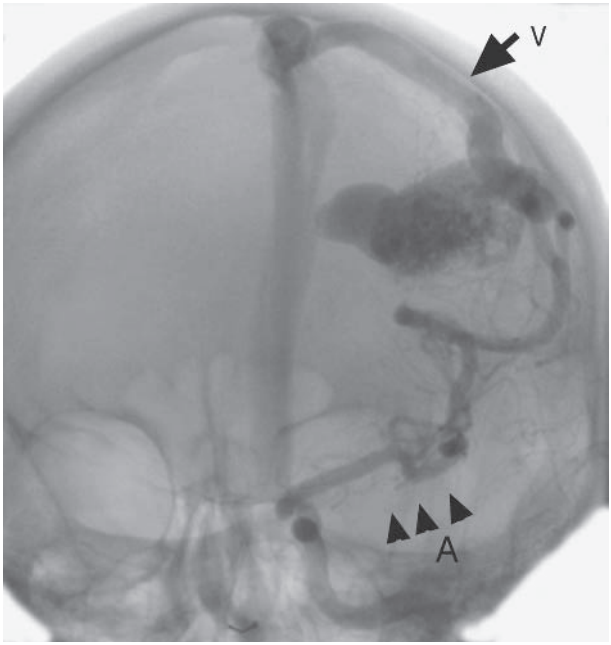

Figure 5.15 Angiogram of arteriovenous malformation. Digital subtraction angiography demonstrates a large AVM in the left parietal lobe, predominantly supplied by the left middle cerebral artery (arrow heads). A large draining vein is seen early in the arterial phase of enhancement (arrow).

- Useful adjunct to surgery or radiosurgery
- Complications due to catheter sticking to fragile vessels, extravasation of glue, infarction, or hemorrhage

Radiosurgery

- High-dose radiotherapy focused on the lesion using a stereotactic frame and delivered in one treatment session
- Gamma knife or Linac-based systems are used to deliver the radiation.
- Advantages: low morbidity, day case procedure
- However, obliteration occurs gradually over 2 years by progressive endarteritis obliterans. During this period the risk of hemorrhage is not reduced.
- Most suited for lesions <3 cm

Cavernous hemangioma (cavernoma) and developmental venous anomaly (DVA)

Cavernomas

- Vascular lesions consisting of large vascular channels with slow blood flow within
- Capillary lesions macroscopically resemble blackberries.
- May be located within the brain or spinal cord or cauda equina
- Familial cases reported, more likely to have multiple cavernomas if familial
- May result from trauma or radiation
- Solitary, 75%; multiple, 25%
- May enlarge

Clinical presentation

- Hemorrhage <1% per annum
- Epilepsy due to epileptogenic hemosiderin leaching out
- Progressive neurological deficits, especially in the posterior fossa and in the spinal cord

Imaging features

- CT: normal in 50%. Well-defined hyperdense lesion with no edema unless acute hemorrhage. Occasional calcification and may or may not enhance (Fig. 5.16)
- MRI (Fig. 5.17): rounded or oval lesion with rim of hypointensity (T1W and T2W) results from hemosiderin due to chronic bleeding. Internal heterogeneous signal on T1W and T2W represents blood products of various ages. T2* hypointense (black) lesion is the most sensitive sequence for detection.
- DSA usually negative

Management

- Accessible lesions can be excised if recurrent hemorrhage.
- Radiosurgery as a treatment option is still controversial.

Developmental venous anomaly (DVA)

- Represent anomalous venous drainage pathways
- Enlarged white matter, often periventricular; veins radiate around a central vein
- May be associated with cavernomas and cortical dysplasia
- Usually asymptomatic lesions found incidentally on CT/MRI

Clinical presentation Rarely hemorrhage except when associated with other vascular lesions.

Imaging features

- CT and MRI: small linear or stellate enhancing lesions with no mass effect (Fig. 5.18).
- DSA venous phase reveals a "Medusa head."

Management

- Previously excised with poor outcomes, as they functionally drain normal brain tissue
- Now considered benign normal variant and left alone

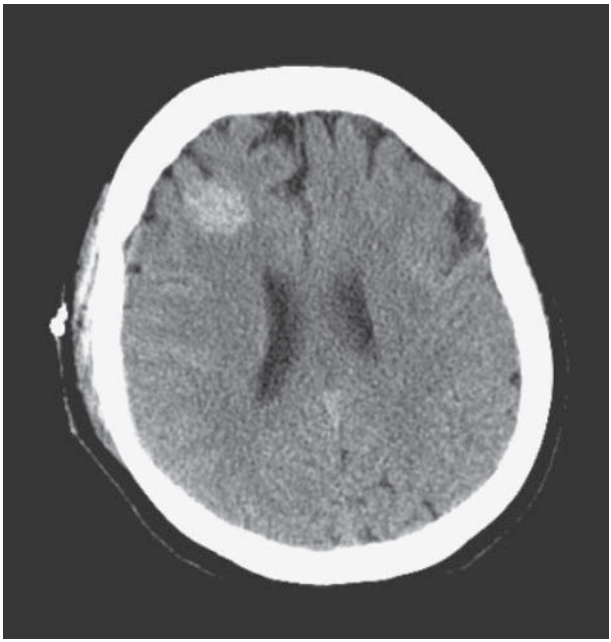

Figure 5.16 CT of cavernoma. Hyperdense rounded mass is seen in the right frontal lobe without mass effect. The features are consistent with a cavernoma.

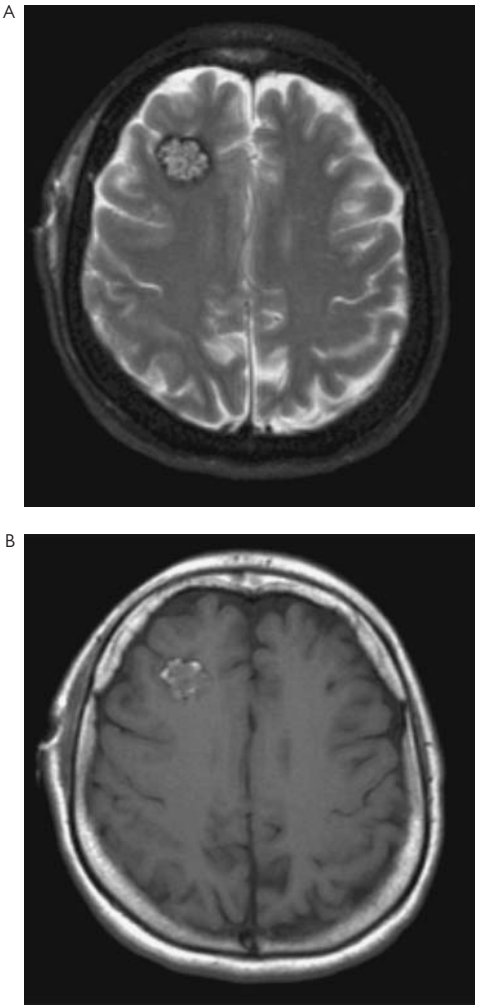

Figure 5.17 MRI of cavernoma. Right frontal cavernoma on MRI. Axial T2 (A) and T1 postcontrast imaging (B) demonstrate characteristic appearance of a cavernoma with a dark hemosiderin rim encasing a coarsened hyperintense signal region in the middle. T1-weighted images also show a characteristic heterogenous lesion with coarse mineralization.

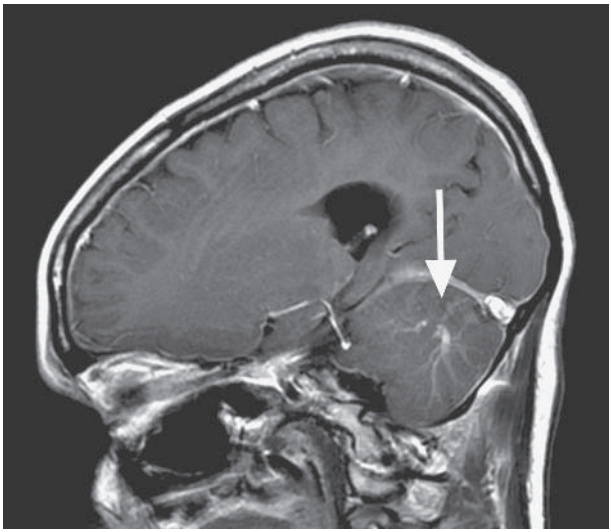

Figure 5.18 MRI of developmental venous anomoly. Sagittal T1 postcontrast image shows a linear enhancing structure in the posterior fossa (arrow) with radiating branches, which is characteristic of a developmental venous anomaly.

Dural arteriovenous fistulae (dAVF)

Cranial dAVF

These occur throughout the neuroaxis. Common sites include anterior fossa floor, adjacent to the major venous sinuses, and the tentorial hiatus.

Clinical features

Presentation is with the following:

- Hemorrhagic stroke
- Progressive neurological deficit due to venous congestion
- Headaches
- Pulsatile tinnitus especially if a bruit is audible
- Seizures

Imaging

- CT/MRI is usually normal unless there is venous occlusion.
- DSA after hematoma resolution, if acute presentation, defines the location, feeding arteries, and venous drainage.

Grading system according to Djinjian and Merland

- Group 1. Blood drains directly into meningeal vein or sinus. Normal direction of flow
- Group 2. Venous reflux into cortical veins
- Groups 3 and 4. Venous reflux is associated with retrograde flow along the venous sinuses.

Group 1 lesions are benign and rarely require treatment to prevent hemorrhage. Other groups are at risk of hemorrhage and likely warrant intervention.

Treatment

- Requires multidisciplinary assessment with neurosurgeon and interventional neuroradiologist.
- Options include occlusion of abnormal fistulous communication between artery and vein by surgery or endovascular techniques using glue occlusion.

Carotid cavernous fistula (CCF)

Subtype of dAVF. Defined as low flow or high flow, traumatic or spontaneous, direct or indirect, aneurysmal or nonaneurysmal.

Clinical features

- Sudden onset, painful, pulsatile exophthalmos and ophthalmoplegia
- Cavernous sinus acts as a barrier and intracranial or subarachnoid hemorrhage does not occur.
- High-flow fistulae occur in young males following trauma or a ruptured aneurysm. Result in a direct communication between internal carotid artery and cavernous sinus.
- Low-flow or indirect fistulae occur in older patients with vascular risk factors. Result from dural fistulae within the walls of the cavernous sinus from branches of the internal or external carotid arteries.

Management

- High-flow fistulae rarely close spontaneously. Closure is with endovascularly released detachable balloons or coils.
- Low-flow fistulae tend to obliterate spontaneously. Conservative management by intermittent massage to occlude the internal carotid artery in the neck. Occasionally, partial embolization of external carotid branches but not internal carotid due to risk of stroke.

Spinal dAVF

- Most common spinal vascular malformation (80%)
- May be acquired secondary to thrombosis of the extradural venous plexus
- Venous hypertension and engorgement result in a subacute necrotizing myelopathy.

Clinical features

- Presents in middle to late age group with a progressive myelopathy (Foix–Alajouanine syndrome)
- Commonly between T5 and L3
- Spinal bruit may be heard.

- Diagnosis should be considered in any patient with a cauda equina lesion with a mixture of upper and lower neuron signs + sphincter involvement.

Imaging features

- MRI may be normal or show nonspecific abnormalities with intramedullary hyperintensity on T2W and hypointensity on T1W.
- Typically involves the conus and lumbar enlargement
- Specific features are the dilated pial veins along the dorsal surface of the cord best seen on T2W images as serpiginous foci of flow void against hyperintense CSF. However, it may be difficult to differentiate from CSF pulsatile flow.
- Gadolinium may reveal serpiginous areas of enhancement.
- MRA with contrast may demonstrate enlarged intradural veins.
- Spinal angiography is gold standard for diagnosis, localization, and treatment.

Management

- Endovascular obliteration using liquid embolic agents such as N-butylcyanoacrylate (NBCA) in >50% of cases
- Can be performed at the time of spinal angiography
- Open surgical intervention to divide the fistulous point under a surgical microscope

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Chapter 6

Epilepsy

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Diana Gomez-Hassan, MD, PhD

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Status epilepticus *195*

Epilepsy: introduction

Epilepsy is defined as an increased tendency to have recurrent seizures, manifested by two or more *unprovoked* events. The etiology of epilepsy may be known (symptomatic epilepsy) or unknown (idiopathic epilepsy). Isolated seizures occurring in the context of an acute illness (e.g., hypoglycemia) should not be considered epilepsy.

Incidence and prevalence

May be estimated at 50/100,000/year; in the United States, the prevalence of epilepsy is estimated at 5–8/1000 (1.5–2 million people affected). A higher incidence and prevalence of epilepsy has been observed in developing countries.

Etiology

The cause of epilepsy remains unknown in nearly 70% of cases. Etiology varies significantly with age. In the United States, epidemiologic studies have estimated the frequency of the following known etiologies:

- Cerebrovascular disease, 13.2%
- Developmental, 5.5%
- Cerebral trauma, 4.1%
- Derebral tumor, 3.6%
- Infection, 2.6%
- Neurodegenerative, 1.8%

Other important causes include hippocampal sclerosis, and cortical and vascular malformations. In the tropics, neurocysticercosis is a common cause.

Classification

Epilepsies are often classified as ***electroclinical syndromes*** with a principal distinction made between ***generalized*** and ***focal (partial)*** onset seizures. Epilepsy may be classified etiologically as follows:

- Idiopathic (possible genetic predisposition with normal development, neurological examination and neuroimaging studies)
- Symptomatic (structural abnormality present on imaging studies)
- Cryptogenic (structural abnormality suspected but not demonstrated)

Classification of epilepsy (modified, abbreviated classification of the International League against Epilepsy)

Generalized epilepsies and syndromes

- Idiopathic with age-related onset:
  - Childhood/juvenile absence epilepsy
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalized tonic–clonic seizures (GTCs) on awakening
- Symptomatic and cryptogenic:
  - West syndrome
  - Lennox–Gastaut syndrome
  - Epilepsy with myoclonic absences

- Symptomatic
  - Myoclonic encephalopathy

Focal epilepsies and syndromes

- Idiopathic with age-related onset:
  - Benign childhood epilepsy with centrotemporal spikes
  - Reading epilepsy
- Symptomatic:
  - Epilepsy with simple partial, complex partial, or secondarily generalized seizures arising from any part of the cortex
  - Epilepsia partialis continua (EPC)
  - Syndromes characterized by specific activation

Undetermined epilepsies and syndromes (focal or generalized)

Epilepsy with continuous spike and wave activity in sleep.

Clinical features

Seizures are paroxysmal, stereotypic events. Diagnosis is clinical; eyewitness accounts are crucial. Seizures usually last only several minutes, but they may be followed by a more prolonged interval of transient drowsiness, confusion, or focal deficits. (See "Loss of consciousness," p. 53.)

Triggers include:

- Alcohol
- Fatigue
- Sleep deprivation
- Infections and fever
- Hormonal fluctuations
- Hypoglycemia
- Stress
- Strobe lighting (photosensitive epilepsy)
- Reading, hot water (rare)

Childhood absences

- Rare after age 10 years
- F > M
- Brief loss of awareness (several seconds) many times a day. Triggered by hyperventilation
- Most cases remit in adulthood.
- EEG characteristic—3 Hz spike and wave, no photosensitivity

Juvenile myoclonic epilepsy (JME)

- Onset before age 30 years
- Myoclonic jerks in the morning
- Typical absences
- Generalized tonic–clonic seizures
- EEG typical with 3–4 Hz generalized spike/wave or polyspike/wave ± photosensitivity
- Remission rare; lifelong pharmacologic treatment usually indicated

Complex partial seizures

- Often associated with underlying structural abnormality, e.g., hippocampal sclerosis (Fig. 6.1), dysembryoplastic neuroepithelial tumor (DNET; Fig. 6.2), cavernous hemangioma, or cortical dysplasia (Fig. 6.3).
- Automatisms (lip smacking, chewing, swallowing, stereotypical hand movements)
- Déjà vu and jamais vu
- Olfactory or gustatory auras (unpleasant)
- Unusual behavior or emotionality

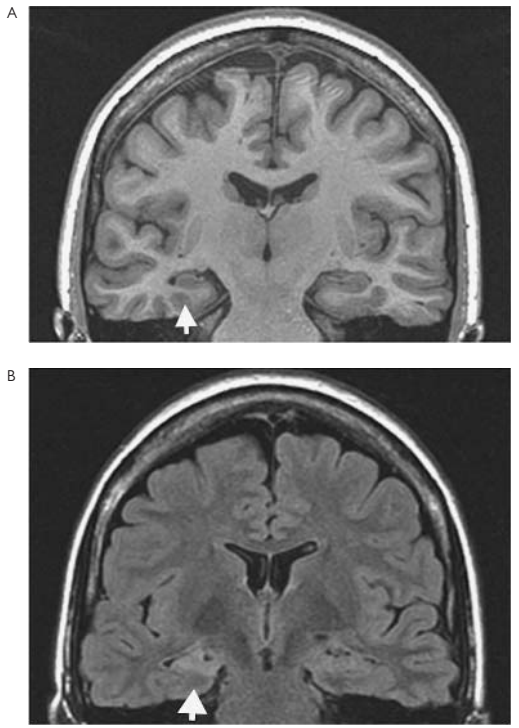

Figure 6.1 MRI of hippocampal sclerosis. Coronal spoiled gradient image (A) shows atrophy of the right hippocampal formation seizures (white arrow) in a patient with refractory complex partial. Coronal FLAIR (B) demonstrates the relatively greater signal hyperintensity in the right hippocampal formation (white arrow) compared to the left.

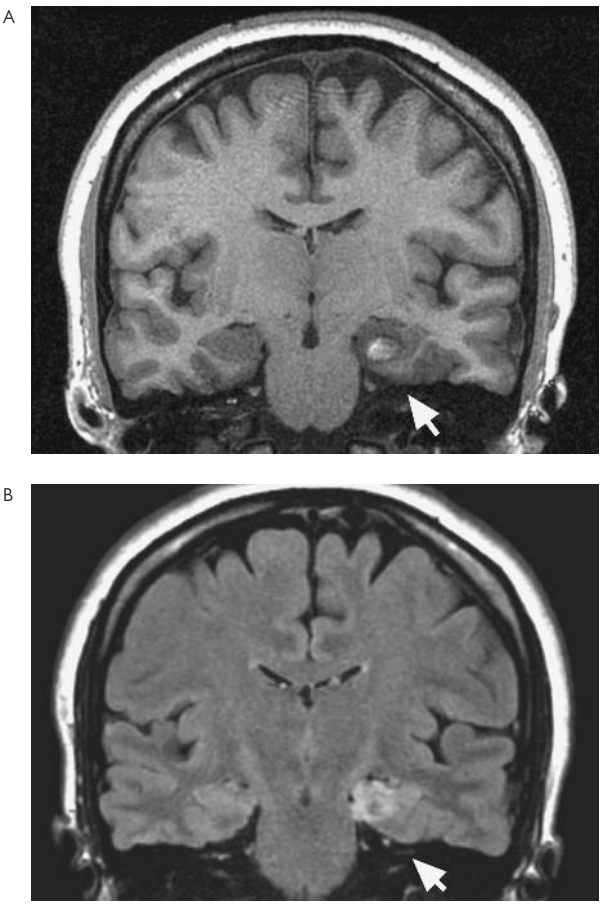

Figure 6.2 MRI of dysembryoplastic neuroepithelial tumor (DNET). Coronal spoiled gradient image (A) identifies a slightly bulky T1 hyperintense lesion within the left hippocampal formation (white arrow). Coronal FLAIR images (B) demonstrates diffuse high signal within the lesion and adjacent hippocampal formation (white arrow) in this patient with a long history of complex partial seizures.

Figure 6.3 MRI of focal cortical dysplasia. Coronal spoiled gradient image (A) demonstrates focal cortical thickening and blurring of the gray–white matter interface along the left paramedian frontal lobe (white arrow). Axial FLAIR images (B) demonstrates associated hyperintense signal associated with this malformation.

Investigations

- Blood investigations:
  - CBC
  - Renal, liver function, calcium, magnesium, glucose
- MRI with specific (coronal) views of both temporal lobes if complex partial seizures
- EEG; consider sleep deprived and prolonged ambulatory recordings if a routine study is negative.

Management of epilepsy

General advice

- Advise the patient not to drive. The seizure-free interval needed for resumption of driving privileges varies according to state legislation. In "mandatory reporting" states the physician must report the event directly to the state attorney-general. In other states, this responsibility is incumbent upon the patient.
- Avoid unsafe activities, i.e., take showers rather than baths, avoid swimming alone, do not use power equipment or work at heights.

Starting treatment

Single seizures

No treatment is indicated unless the EEG or MRI reveals an abnormality that suggests a high risk of recurrence. If precipitating factors (e.g., sleep deprivation, alcohol) are identified, avoidance or abstinence should be recommended.

After a single unprovoked seizure, the risk of recurrence is 24% with no focal neurologic abnormality and a normal EEG, and 65% if associated with focal findings on examination or MRI, and an abnormal EEG.

Prophylaxis

There is no indication for starting treatment in patients with head injuries, craniotomy, and brain tumors, unless seizures actually occur.

Drug treatment (see Tables 6.1 and 6.2)

Aim of treatment is to render the patient seizure free with minimal side effects. Other complications include sudden unexpected death in epilepsy (SUDEP)—1/200/year in refractory epilepsy.

- Factors to be taken into account when choosing treatment:
  - Age
  - Sex
  - Type of epilepsy
  - Other drugs, e.g., oral contraceptives (OCPs)
  - Other medical conditions, e.g., liver or renal dysfunction
- Therapy is initiated at a low dose gradually titrating to an effective level to avoid side effects ("start low, go slow").

Table 6.1 First- and second-line drugs for different types of epilepsy

Type of epilepsy	First-line drugs	Second-line drugs
Generalized	Valproate or lamotrigine	Levetiracetam or topiramate
Focal	Carbamazepine, oxcarbazepine, lamotrigine, or levetiracetam	Topiramate, pregabalin, or valproate
Additional myoclonus	Valproate or lamotrigine	Levetiracetam or zonisamide
Absence	Valproate, lamotrigine, or ethosuximide	

Table 6.2 Antiepileptic drugs: dosages and side effects

AED	Dose	Side effects
Carbamazepine (XR form)*	Start 200 mg bid. Increase by 200 mg at Q7D until control achieved. Usual adult target dose 400–1200 mg/day	Rash, neutropenia, hyponatremia, Stevens Johnson syndrome, osteoporosis, numerous drug interactions. May make myoclonus worse. Liver enzyme inducing. Will reduce efficacy of oral contraceptive pills (OCPs)
Oxcarbazepine*	Start at 300mg bid; increase at 300 mg Q7D to 1200–1800 mg/day	Hyponatremia, rash, Stevens Johnson syndrome. Mild induction of hepatic enzymes. Will reduce efficacy of OCPs
Sodium valproate*	Start at 250 mg tid, increase by 250 mg Q7D to 900–2500 mg/day	Rash, tremor, weight gain, hair loss, menstrual changes, thrombocytopenia, hyperammonemia, pancreatitis
Lamotrigine	Start 25 mg/day as monotherapy; increase by 25 mg Q7D to 200–400 mg/day. If adjunct to valproate, start 25 mg alternate days for 2 weeks, increase by 25 mg Q14D to 200–400 mg/day	Rash, Stevens-Johnson syndrome, toxic epidermolysis. Risk of adverse events increased with valproic acid.
Topiramate	Start 25 mg/day; increase by 25 mg Q7–14 D as tolerated to 200–400 mg/day	Weight loss, cognitive impairment, renal calculi, metabolic acidosis

Table 6.2 (*Contd.*)

AED	Dose	Side effects
Levetiracetam	Start 250 mg bid, increase by 250–500 mg Q7D as tolerated to 1000–4000 mg/day	Drowsiness, irritability, mood swings
Pregabalin	Start 50 mg tid; increase by 50 mg Q7–14D to 200 mg tid	Weight gain, peripheral edema
Phenytoin*	Start 300 mg/day, then monitor levels increasing dosage as needed by 50–100 mg Q7D. Note: Zero-order kinetics: small dose increase may produce large changes in levels	Gum hypertrophy, acne, hirsuitism, coarse facies, osteoporosis, ataxia

*Assess CBC, electrolytes, and LFTs when initiating treatment and at 6–12 month intervals during therapy.

- If seizures continue, increase dose as tolerated. If seizures persist, transition to another first-line drug.
- If anticonvulsant monotherapy is unsuccessful, adjunctive treatment with a second-line drug should be considered.

Drug monitoring

Measuring drug levels is indicated in the following situations:

- Suspected poor or erratic compliance
- Symptoms of toxicity, e.g., nausea, ataxia, confusion, diplopia
- There is little correlation between blood levels and therapeutic effect for many newer anticonvulsants (e.g., lamotrigine, oxcarbazepine, topiramate, levetiracetam), so routine therapeutic monitoring of blood levels is unhelpful.

Prognosis with drug treatment

By 12 months 60%–70% of treated patients will be seizure free. After 2 years, withdrawal of drugs can be considered. Predictive factors for relapse include the following:

- Syndromic epilepsy, e.g., JME
- Underlying structural pathology
- Continued epileptiform abnormality on EEG
- Severe prolonged epilepsy before remission
- Increased age

Factors that may affect the decision to stop include driving. Patients are advised to stop driving during drug withdrawal and for 6 months thereafter.

Resective surgery

Any patient with focal epilepsy who has failed two or more trials of anticonvulsant therapy should undergo inpatient video/EEG monitoring and other evaluations (high-resolution MRI, neuropsychological testing, and sometimes further neuroimaging studies (e.g., ictal SPECT, FDG-PET; see Fig. 6.2) in order to determine whether they are candidates for resective surgery.

Patients with certain structural neuroimaging findings (e.g., mesial temporal sclerosis; Fig. 6.1), DNET (Fig. 6.2), or cavernous hemangioma may have a high (up to 80%) probability of seizure remission following surgery. Resective procedures are most commonly performed on the temporal lobes. In the nondominant hemisphere, an anteromesial resection including the anterior temporal neocortex, amygdala, and hippocampus may be performed (Fig. 6.4). In the dominant hemisphere, more selective resections of the mesial temporal structures are often performed to spare language function.

In the absence of structural brain pathology, implantation of intracranial electrodes (Fig. 6.5) may be required to delineate ictal onset and permit functional mapping studies.

Vagus nerve stimulation

In patients with medically refractory epilepsy who are not good candidates for surgical resection, vagus nerve stimulator (VNS) therapy may be considered. The vagus nerve stimulator is an implantable medical device consisting of a battery and generator unit, which is usually implanted subcutaneously under the left clavicle, with two wire leads that are tunneled under the skin of the neck. A second incision allows attachment of the terminals of these leads to the vagus nerve trunk. Once implanted, the device is programmed externally to deliver regular stimulation to the nerve, and it may be activated by the patient using a magnet. Although complete remissions are unusual, many patients with severe inoperable focal and generalized epilepsy experience significant improvement, with minimal surgical risks at the time of implantation and few adverse effects apart from transient hoarseness during activation.

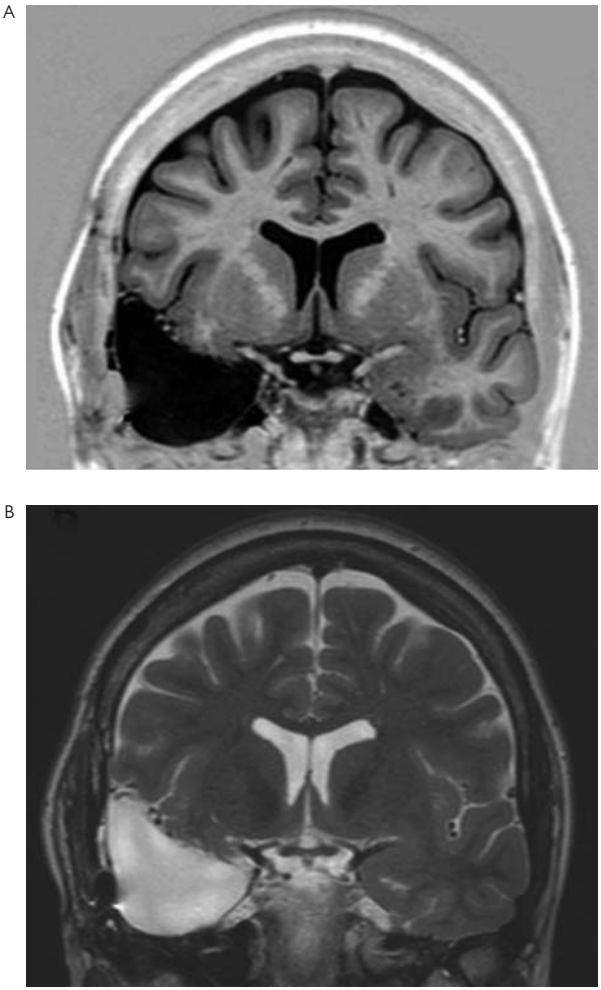

Figure 6.4 MRI of patient status post anterior temporal lobectomy. (A) Coronal spoiled gradient image (B) and coronal T2-weighted image demonstrate the surgical defect in the right middle cranial fossa.

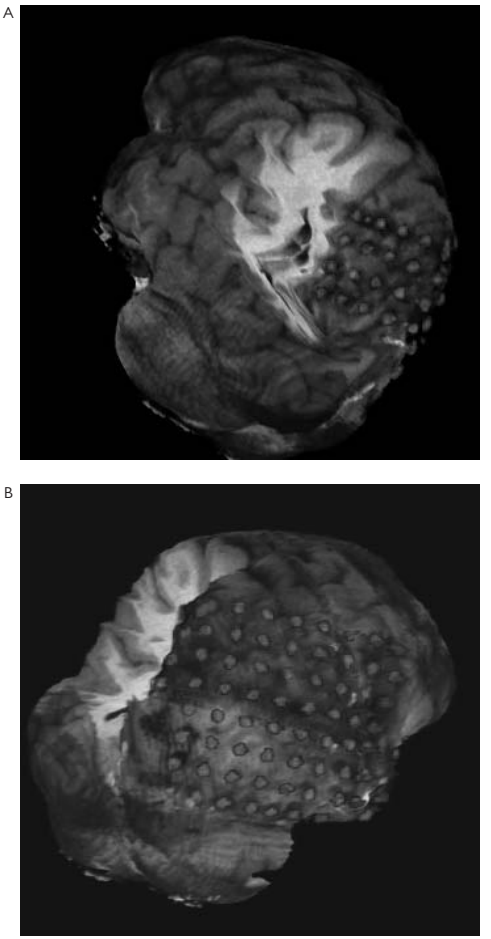

Figure 6.5 (A) MRI coregistration of subdural grid electrode array placement. Obliquely oriented image of the posterior quadrant of the right hemisphere (with the left posterior quadrant subtracted) demonstrates placement of 4 x 5 subdural grid electrode array over the right mesial occipital region. (B) MRI coregistration of subdural grid electrode array placement. Image of the posterior right hemispheric convexity illustrates the placement of a larger 8 x 8 subdural grid array for extensive coverage of the right occipital, parietal, and posterior temporal regions. (Coregistered images provided by Dr. Chuck Meyer, Department of Physics, University of Michigan.)

Women and epilepsy

Contraception

- Anticonvulsants that induce hepatic enzymes (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, and topiramate) all reduce estrogen/progesterone levels and increase the risk of OCP failure. Valproic acid and levetiracetam do not appreciably alter serum estrogen/progesterone.
- Reduced OCP efficacy may be addressed by high estrogen (at least 50 μg) preparations, conversion to depo provera, or another method of contraception.
- OCPs induce the metabolism of lamotrigine, potentially indicating an increase in dosage.

Fertility

- Women with epilepsy have lower fertility rates due to multiple factors, e.g., sexual dysfunction in those with TLE.
- Valproic acid is associated with polycystic ovarian syndrome.

Pregnancy

- Preconception counseling is essential.
- There is a 4%–6% probability of fetal malformation with anti-epileptic drugs (AEDs) taken in the first trimester; highest risk with valproic acid and anticonvulsant polytherapy.
- Every effort should be made, where possible, to use anticonvulsant monotherapy at the lowest effective dose.
- Folic acid (4 mg/day) should be taken by all women of childbearing age who are on anticonvulsant therapy, in order to minimize risk of fetal malformation.
- Patients who become pregnant on AEDs should have increased obstetrical surveillance (ultrasound, alpha fetoprotein levels) for fetal malformation.

Epilepsy during pregnancy

- Thirty percent of women will experience significant improvement in their epilepsy during pregnancy, with some patients becoming transiently seizure free. Thirty percent of patients will have increased seizure frequency during pregnancy, with the most exacerbation seen in the late first and early second trimesters.
- Clearance of hepatically metabolized AEDs (phenytoin, carbamazepine, valproic acid, lamotrigine, topiramate) is increased during pregnancy, sometimes necessitating dosage increases. Free (unbound) levels of highly protein-bound drugs (phenytoin, carbamazepine, valproate) should be measured due to increased volume of distribution. Clearance of renally eliminated drugs (levetiracetam) is also often increased. Following delivery, readjustment of AED dosages is often needed.
- New onset seizures during pregnancy demand investigation. Potential serious etiologies include:
  - Eclampsia
  - Neoplasms, especially meningioma

- Subarachnoid hemorrhage
- Arteriovenous malformation
- Arterial/venous thrombosis

Patients taking enzyme inducing AEDs (phenytoin, carbamazepine, phenobarbital) during pregnancy should be treated with vitamin K, 20 mg/day beginning in the 36th week of pregnancy to prevent hemorrhagic disease of the newborn.

The risks of breast feeding during AED therapy remain unknown for most agents. The exceptions are phenobarbital, primidone, and benzodiazepines, which are present in high concentrations in breast milk and which can produce significant neonatal lethargy and irritability. In all instances, the potential benefits of breast feeding (bonding between mother and infant, transfer of passive immunity) must be weighed against the potential risks of nursing with maternal anticonvulsants.

Psychogenic seizures

Often referred to as "nonepileptic seizures" or "pseudoseizures," these events are often confused with epilepsy, usually to the detriment of the patient. Individuals with psychogenic seizures frequently undergo unnecessary therapy with anticonvulsant drugs with the attendant short-term and long-term adverse events, and they are also occasionally intubated and monitored in the intensive care unit ("pseudostatus"). This problem is complicated by the fact that 50% of patients with psychogenic seizures may have epilepsy as well.

Clinical features of psychogenic seizures

- May be found in 10%–30% of patients referred to tertiary care centers for evaluation of refractory epilepsy
- History of childhood physical and/or sexual abuse.
- Triggered by stress
- Not responsive to multiple trials of AEDs
- Frequent admissions to hospital
- Certain characteristics of the attacks may suggest the diagnosis (Table 6.3), although inpatient video EEG monitoring is usually definitive.

Management

- Establish diagnosis with certainty.
- Explain that the attacks are an unconscious response to some form of stress.
- Relaxation techniques and cognitive-behavioral therapy are the most appropriate treatments, although other psychiatric comorbidity (e.g., depression) often has to be addressed.
- Response to therapy is optimal when the history of psychogenic attacks is relatively brief.
- Consider gradual withdrawal of AEDs if there is low suspicion of coexistent epilepsy.

Table 6.3 Characteristics of psychogenic seizures compared with those of epileptic seizures

Characteristic	Psychogenic seizures	Epileptic seizures
Triggered by anger, panic, suggestion	Common	Rare
Onset	Gradual	Sudden
Duration	Prolonged, hours	Minutes
Breathing	Continuous	Apneic
Color	Normal	Cyanosed
Retained consciousness	Yes, response to pain is often preserved; a dropped arm will usually avoid striking the face.	Rare
Unusual movements	Pelvic thrusting, back arching, erratic movements. Movements of limbs are asynchronous.	Rare Movements of the limbs during the convulsion are synchronous.
Eyes	Resistance to forced eye opening	No resistance
Occur in company	Common	Unusual
Tongue biting	Rare	Common
Self-injury	Rare	Common
Incontinence	Rare	Common
Postictal confusion	Rare	Common
Prolactin levels before and 20 minutes after	No elevation	Elevation (2.5x control) but may be normal after prolonged status or partial seizures
Postictal EEG	Normal	Slowing, suppression

Status epilepticus

Status epilepticus occurs in the United States at a rate of 50 per 100,000 persons per year. It is defined as consecutive seizures without complete interictal recovery, or as a single prolonged seizure lasting longer than 5 minutes. It is a neurological emergency with an overall mortality of over 20%.

Clinical presentations

Approximately 80% of cases present as generalized tonic clonic status epilepticus. Other subtypes are important; complex partial status epilepticus and absence status epilepticus may present as prolonged confusional states.

Twelve percent of cases of status epilepticus are new presentations of epilepsy in patients with no prior history of seizures.

Generalized tonic clonic status epilepticus exhibits two stages of evolution: a prodromal phase, in which discrete seizures occur with increasing frequency and duration; and a second phase, in which clinical seizure activity becomes less conspicuous despite continuous electrographic seizure activity (electromechanical dissociation).

Management of prodromal phase

- Maintenance of airway, oxygenation, and blood pressure. Consider intubation for airway protection.
- Establish IV access.
- Obtain blood for CBC, serum glucose, electrolytes, toxicology screen, and AED levels.
- Monitor vital signs closely.
- If serum glucose is not immediately available, administer 100 mg IV thiamine, followed by 50 mL of D50 IV.
- Administer 0.1 mg/kg of lorazepam IV to a maximum of 8 mg or 0.2 mg/kg of diazepam IV (may be repeated once after 5 minutes).

Management of established generalized tonic/clonic status epilepticus

- Administer 20 mg/kg phenytoin equivalent of fosphenytoin; deliver no more rapidly than 150 mg/min; monitor EKG and blood pressure throughout the infusion.
- If overt convulsive activity is no longer present, begin continuous EEG monitoring, if available.
- When status continues beyond first IV fosphenytoin infusion, administer additional doses of fosphenytoin at 5 mg to a total maximum dose of 30 mg/kg.
- If status persists, intubate patient and initiate mechanical ventilation if this has not already been done.
- Administer 20 mg/kg of phenobarbital IV at 100 mg/min.
- Consider investigations to reveal etiology of status epilepticus:
  - CT scan or MRI
  - CSF examination
- Reinstate any withdrawn AED.

Management of refractory status epilepticus

- The patient should by now be intubated, mechanically ventilated, and transferred to an intensive care environment where invasive hemodynamic monitoring can be instituted.
- Administer midazolam at a loading dose of 0.2 mg/kg, followed by a maintenance dose of 0.75–10 μg/kg/min. Alternatively, propofol can be given at a loading dose of 1–2 mg/kg IV, followed by a maintenance infusion of 2–10 mg/kg/hr. In both instances, the dosage of anesthetic agent should be titrated to a burst suppression pattern on the EEG if the agent is well tolerated hemodynamically, or to suppression of electrographic seizure activity if hemodynamic instability is encountered.

- Anesthesia may be cautiously withdrawn after an interval of 12–24 hr; if seizures recur, further 12–24-hour intervals should be administered until remission is obtained.
- Treat medical complications (infection, acidosis, electrolyte derangements, uremia, hypoglycemia) aggressively, as they will tend to make status epilepticus highly resistant to treatment.

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Chapter 7

Migraine

Lawrence P. Hudson, MD

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Migraine: introduction and clinical features

Epidemiology

- Migraine is a common episodic neurological condition. It occurs in up to 11% of the adult population, usually with onset in late adolescence or the early third decade. Approximately 70% of migraine sufferers are females.
- There is a tendency for migraine to become less severe or even remit in the fifth and sixth decades.
- Forty-six percent of patients have a family history of migraine. The risk of a child developing migraine is about 70% if both parents are affected, and 45% when one parent is affected.

Pathophysiology

Migraine is most accurately thought of as a primary disorder of the brain produced by dysfunctional brainstem regulation of craniovascular afferents. In a genetically predisposed individual, activation of the trigeminovascular network in the dorsal midbrain and dorsolateral pons presumably causes: (a) impaired regional blood flow to the brain, (b) perimengeal vasodilatation and neurogenic inflammation, and (c) cortical spreading depression, thought to be responsible for the migraine aura. The importance of genetics is underscored by the discovery of a mutation on chromosome 19 that codes for a subunit of the voltage-gated calcium channel in familial hemiplegic migraine, an unusual migraine variant. It has been hypothesized (but not proven) that other forms of migraine may be channelopathies as well.

Clinical features

- A migraine attack can be divided into four components: prodrome, aura, headache, and resolution.
- The occurrence of an aura distinguishes two major types of migraine episode: Migraine with aura ("classic migraine") and Migraine without aura ("common migraine").
- Attacks may last from 4 to 72 hours and are recurrent, supporting the concept of migraine as a chronic episodic disorder.
- Prodromal symptoms may include somnolence, heightened alertness, anxiety or hunger.

Migraine aura

- The aura is variable in presentation, but most often is characterized by visual phenomena such as fortification spectra, scotomata, scintillating scotomata, as well as visual or auditory hallucinations. Less commonly, visual distortions such as macropsia and micropsia may be described. Somatosensory phenomena, usually paresthesias, are also commonly encountered. Hemiparesis, sometimes with a "march," olfactory and gustatory hallucinations, and distortions of body image are unusual but sometimes reported.
- The aura may occur without evolution into a headache; this is referred to as "migraine equivalent."

Headache phase

- Headache may be unilateral, bilateral, or shift sides during the course of an attack. It is often throbbing in character, although it may be more continuous and felt in a periorbital or retroorbital distribution. There is often a "referred tension" component, with occipital and cervical pain being prominent.
- Most important associated features include exacerbation by routine physical activity, nausea, vomiting, photophobia, and phonophobia.

Migraine triggers

- Stress and relaxation after stress
- Sleep: sleep deprivation, "sleeping in," interruption of usual sleep pattern
- Trauma and mild closed head injury
- Sensory stimulation: glare, flickering lights, smells (e.g., certain perfumes)
- Irregular eating habits: missing a meal (hypoglycemia)
- Foods: red wine, cheese, chocolate, caffeine
- Food additives: monosodium glutamate
- Exercise
- Excessive heat and dehydration
- Drugs: vasodilators such as nitroglycerin
- Changes in barometric pressure such as those preceding a thunderstorm

Migraine variants

Basilar migraine: Usually characterized by a visual prodrome, followed by ataxia, vertigo, diplopia, tinnitus, and nausea/vomiting. Objectively, nystagmus, dysarthria and altered level of consciousness may be present. Sometimes may present as an acute confusional episode, often in children.

Hemiplegic migraine: Usually begins in childhood and remits in adulthood; may be sporadic or familial. Hemiplegia may last less than 1 hour, or it can persist for days to weeks. Attacks are often precipitated by minor head injury, and changes in consciousness may be present. Many cases of familial hemiplegic migraine have been mapped to chromosome 19p13 (see earlier section, "Pathophysiology").

Status migrainosus: Attacks of migraine lasting longer than 72 hours, usually with prolonged nausea and vomiting.

Ophthalmoplegic migraine: Migrainous headache with 3rd or 6th nerve paresis, which may persist for days to weeks, sometimes requiring exclusion of intracranial hypertension or aneurysm.

Other disorders presenting as migraine

CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy); mapped to chromosome 19

MELAS (Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes)

Migraine: differential diagnosis, investigations, and International Headache Society (IHS) criteria

Differential diagnosis

- Acute headache occurs in 15% of patients with TIA, 25% with acute ischemic stroke, 50% with acute intracerebral hemorrhage.
- Clinical differentiation of migraine headache from other, potentially malignant causes of headache is essential.
- Most patients presenting with initial onset of severe headache not clinically typical of migraine, or with focal neurological symptoms or signs will require further investigation, including neuroimaging studies and possibly lumbar puncture.
- Patients with established migraine developing headache departing in character from previous attacks also may need investigation.
- Other causes of headache with focal neurological disturbance:
  - SAH
  - Cerebral infarction, hemorrhage, venous thrombosis
  - Dissection of the carotid and vertebral arteries
  - Neoplasm, abscess
  - Meningoencephalitis (a mild lymphocytic pleocytosis may be seen during an acute migraine attack)

Investigations

Imaging studies detect a significant abnormality in <0.5% patients with migraine and a normal neurological examination, and are not usually indicated. MRI scans in migraine patients, with and without auras, may reveal small nonspecific white matter lesions in 30% of individuals under the age of 40 years. Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) are useful in identifying acute arterial occlusion, aneurysm, and venous sinus thrombosis.

Abbreviated International Headache Society (IHS) criteria for migraine

Migraine without aura ("common migraine")

At least five attacks fulfilling criteria a–d:

a. Headache lasting 4 hours to 72 hours
b. Nausea/vomiting and/or light and noise sensitivity
c. Two of the following:
   - Unilateral pain
   - Moderate or severe intensity pain
   - Aggravation by simple physical activity
   - Pulsating pain
d. Not attributable to another disorder

Migraine with aura ("classic migraine")

At least three of the following:

- Reversible focal brainstem or cortical dysfunction
- Aura develops over >4 minutes or two or more symptoms occur in succession
- Each aura <60 min
- Headache <60 min following aura

Suggested criteria for chronic or transformed migraine

- Daily or almost daily (>15 days/month) head pain >1 month
- Average headache duration > 4 hours/day (untreated)
- At least one of the following:
  - A previous history of IHS migraine
  - History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months
  - Current superimposed attacks of headache that meet all the IHS criteria except duration

Migraine therapy

Choice of therapy is governed by frequency and severity of attacks, associated symptoms, responses to prior treatment, coexistent disorders, and adverse events.

Acute (abortive) migraine therapy

Simple analgesia with antiemetics

Useful only if nausea and vomiting are not major symptoms during a migraine attack; effect may be limited by reduced gastric motility.

Acetaminophen, 500–1000 mg or an NSAID (ibuprofen, naproxen, diclofenac) + metoclopramide, 10 mg.

Triptans (selective 5-HT$_1$ antagonists)

- All drugs of this class (sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan; see Table 7.1) have a high efficacy with up to 70% having a response within 2 hours and 40% being pain free at 2 hours.
- Zolmitriptan and rizatriptan are available as wafers but do not have a more rapid onset of therapeutic effect.
- Sumatriptan is available as nasal spray and injection.
- Early therapy will optimize therapeutic response.
- Headache recurrence within 12–24 hours occurs in 30% of patients; a second dose of triptan may be attempted. If this is ineffective, administration of a "rescue medication" such as a narcotic analgesic, NSAID, corticosteroid, or neuroleptic may be considered (Table 7.2).
- If two trials of a particular triptan at high therapeutic doses are unsuccessful, a trial of another triptan should be considered.
- Overuse may result in rebound headaches in 10% of patients.
- Contraindications include coronary artery disease, cerebrovascular disease, uncontrolled hypertension, peripheral vascular disease, significant hepatic impairment, and pregnancy.
- Common adverse effects include chest discomfort or heaviness; jaw, shoulder, and neck tightness; paraesthesias, fatigue, and dizziness.
- Concurrent MAOI administration is *contraindicated.* Serotonin syndrome is an occasional adverse event.

Ergotamine preparations

- Ergotamine tartrate is still sometimes useful in patients who do not respond to triptans and who do not have any contraindications to treatment with vasoactive medications. A dosage of 1–2 mg alone or in combination with caffeine may be given orally at onset. It may also be administered by inhaler or suppository.
- Overdosage results in nausea, rebound headache, and peripheral vasoconstriction. The recommended maximum dose per week is 10 mg.
- Dihydroergotamine (DHE) is used intravenously in patients with intractable migraine or status migrainosus at doses of 0.3–1.0 mg every 8 hours up to a total dose of 10 mg.

Table 7.1 Triptan characteristics and dosages

More rapid onset	Lower recurrence rate, lower side effects
Sumatriptan, 50–100 mg po 6 mg SC 5–20 mg IN Max daily dose 12 mg SC/300 mg po	Naratriptan, 2.5 mg Max daily dose 5 mg po
Rizatriptan, 5–10 mg po Max daily dose 30 mg po	Frovatriptan, 2.5 mg Max daily dose 7.5 mg po
Zolmitriptan, 2.5–5 mg po 5 mg IN Max daily dose 10 mg po, 10 mg IN	
Almotriptan, 6.25–12.5 mg po Max daily dose 25 mg po	

Table 7.2 Other abortive agents

Agent and starting dose	Maximum dosage/24 hours
Ergotamine 1–2 mg po/sl/pr	6 mg po/sl/pr
Dihydroergotamine .25–1 mg IM/IV 1 mg SC 2–3 mg IN	2 mg IV 3 mg SC/IM 6 mg IN
Naproxen 275–825 mg po	1650 mg po
Ibuprofen 200–400 mg po	1200 mg po
Ketolorac 10 mg po 30–60 mg IM	40 mg po 120 mg IM
Midrin (acetaminophen/ dichlorophenazone/ somaehtheptene mucinate) 2 caps po then 1 cap Q1H	8 caps
Dexamethasone 4–8 mg po	30 mg po
Prednisone 40–100 mg po	200 mg po
Oxygen 7–10 L/min for 15 min by mask	

Migraine prophylaxis

- Prophylactic therapy should be considered if more than two attacks per month are reported, or if attacks become markedly debilitating.
- A headache diary is useful to monitor frequency and patterns, including relationship to menses, sleep patterns, and other triggers. It is critical to determine if analgesic or triptan overuse is ongoing; these problems will render prophylaxis ineffective.
- Prophylactic drug therapy includes (see Table 7.3):
  - Beta-blockers
  - Tricyclic antidepressants
  - Anticonvulsants
  - Calcium channel antagonists (less effective than other prophylactic regimens but useful when other agents are contraindicated)

Table 7.3 Prophylaxis of migraine headache

Drug	Contraindication	Dose (mg)	Side effects	Comments
Beta blockers	Asthma, peripheral vascular disease, pregnancy			
Nonselective				
Propranolol		40–320	Postural hypotension, fatigue, cold limbs, vivid dreams	Long-acting preparation available
Timolol		10–60		
Nadolol		20–240		
Selective				
Metoprolol		50–450		LA preparation
Atenolol		50–200		
Calcium channel antagonists	Heart block, atrial fibrillation, heart failure			
Verapamil		120–720	Dizziness, constipation	SR Preparation
Diltiazem		90–180		
5-HT2 antagonists				
Cyproheptadine		4–36	Weight gain	Single noctural dose

Table 7.3 (*Contd.*)

Drug	Contraindication	Dose (mg)	Side effects	Comments
Tricyclic Antidepressants	Pregnancy, cardiac conduction defects			
Nortryptylline		10–150	Dry mouth, drowsiness,	Useful if tension headache as well. Combine with beta-blocker
Amitriptyline		10–150	Postural hypotension	
Anticonvulsants				
Sodium valproate	Pregnancy, liver disease	500–1500	Weight gain, alopecia, liver dysfunction, tremor, pancreatitis, polycystic ovaries	Long acting (LA) preparation
Topiramate	Pregnancy	25–100	Weight loss, impaired memory and concentration, acute glaucoma	
Gabapentin	Pregnancy	900–4800	Fatigue, dizziness, diplopia, ataxia	

Migraine and women

Menstrual migraine

- Sixty percent of women report an increase in migraine frequency around menstruation; 14% have migraine exclusively related to the menstrual period.
- IHS criteria identify menstrual migraine as attacks without aura, occurring on days –2 to +3 of the cycle in two-thirds of cycles.
- The hormonal stimulus is thought to be exposure to high estrogen levels, followed by the sharp decline in estrogen immediately prior to ovulation. Estrogen may increase the sensitivity of some 5-HT receptors. Release of uterine prostaglandins at the time of menstruation may also play a role in the development of migraine.

Management of menstruation-related migraine

- Acute (abortive) therapy of attacks is identical to abortive therapy of acute nonmenstrual migraine (Tables 7.1 and 7.2). Because of the episodic and relatively predictable occurrence of these headaches in many patients, perimenstrual prophylaxis is often recommended.

Nonhormonal prophylaxis

- NSAIDS:
  - Naproxen 550 mg daily beginning 2 days prior to predicted menstruation and continuing for 3 days into period.
- Triptans:
  - Frovatriptan 2.5 mg bid for 6 days starting 2 days prior to anticipated onset of menstruation.
  - Naratriptan 1 mg bid for 6 days, starting 2 days prior to onset of menses.

Hormonal prophylaxis

- Continuous hormone treatment has been recommended by many experts in place of 21/7 day regimens because of the tendency of estrogen withdrawal after several weeks to provoke relapse. Unfortunately, there are presently no clinical trials or guidelines documenting the safety or efficacy of this approach.
- The most common agent used for hormonal prophylaxis is perimenstrual estrogen, given as estradiol gel at a dose of 1.5 mg, or transermal estrogen 100 μg, to be given 3 days prior to onset of menses and then continued for 1 week.
- Combination oral contraceptive pills (OCPs) may also be given; if a 1-week hormone-free interval after a 3-week cycle is consistently associated with recurrent headache, three consecutive hormonal cycles can be attempted, followed by 1 week of hormone withdrawal.

Migraine, contraception, and stroke

- Migraine can worsen, improve, or remain unchanged when patients are prescribed the OCP.
- Migraine may begin de novo when a woman starts OCPs. It is not essential to stop the pill at the first migraine attack, since headaches may improve over a number of cycles. OCPs should, however, be stopped if a new headache type develops, or if a new onset migraine aura is encountered. They should also be stopped if typical headaches become unusually intense and/or prolonged.
- The risk of ischemic stroke in young women under age 45 years rises from 5–10 per 100,000 to 17–19 per 100,000 in migraineurs. The risk is further elevated in patients who have migraine with aura. OCPs are contraindicated in patients having migraine with aura, and in individuals having migraine and other independent risk factors for ischemic stroke (hyperlipidemia, hypertension, prothrombotic states, smoking, and right to left cardiac shunts).

Migraine, the menopause, and hormone replacement therapy (HRT)

- At menopause, migraine improves in 65%, worsens in 10%, and is unchanged in 25% of afflicted patients.
- Migraine worsens in most patients subjected to surgical menopause, suggesting estrogen withdrawal exacerbates migraine.
- Hormone replacement therapy, when indicated for menopausal symptoms, may either improve or exacerbate migraine.

- Exacerbation of migraine with HRT may be relieved by reducing the dosage of estrogen, changing to a continuous regimen in patients developing symptoms during the withdrawal phase, or eliminating progesterone, although this will mandate surveillance for endometrial carcinoma.

Migraine and pregnancy

- Eighty percent of patients with migraine experience a reduction in attack frequency during pregnancy.
- Migraine without aura patients may experience auras for the first time in pregnancy; if this occurs, or if there is a change in attack characteristics, it is prudent to evaluate the patient for the possibilities of venous sinus thrombosis, arteriovenous malformation, or incipient eclampsia.

Management of migraine in pregnancy

Nonpharmacologic management

- Avoid pregnancy-related nausea and vomiting resulting in hypoglycemia and dehydration.
  - Eat small, frequent carbohydrate snacks
  - Maintain adequate fluid intake and regular sleep patterns
- Acupuncture and relaxation techniques may be helpful.

Pharmacologic management

- Prophylactic drugs should be discontinued in women planning to conceive.
- Acute treatment:
  - Acetaminophen: safe in all trimesters and during lactation
  - ASA should be avoided due to risk of hemorrhage, premature closure of ductus arteriosus, and Reye syndrome if used during lactation. Nonsteroidal anti-inflammatory agents should be avoided for similar reasons, and ergotamine preparations are specifically contraindicated in pregnancy. 5-HT1 antagonists (triptans) have not yet been demonstrated to be safe in pregnancy.
  - The safest abortive therapy during pregnancy is probably a low-dose narcotic analgesic in combination with an antiemetic; prochlorperazine appears to be relatively safe and effective.

Primary short-lasting headaches

Paroxysmal hemicrania

- Rare disorder with a female/male ratio of 7:1; manifested by severe unilateral headache with nasal congestion, lacrimation, ptosis, and eyelid edema. Episodes average 13 minutes in duration and may occur 10–20 times a day. They may be precipitated by head movement, as well as rotation of the head or neck flexion.
- Important differential diagnosis for cluster headache; chronic paroxysmal hemicrania occurs much less frequently and attacks are shorter and more frequent.

- Patients prefer to sit quietly, behavior that is rare in cluster headache.
- The diagnosis may be supported by a rapid and dramatic response to indomethacin at an initial dose of 25 mg tid; this may be increased to a maximum of 75 mg tid as needed. A proton pump inhibitor may be required to control GI side effects.
- Imaging studies and other investigations are mandated to exclude causes of symptomatic illness such as frontal lobe tumors, idiopathic intracranial hypertension, and collagen vascular disease.

Cluster headache

Epidemiology

Prevalence is lower than for migraine, with an incidence of 0.01%, and higher frequency in Caucasian males. The male to female ratio is approximately 2.1:1. Onset is usually seen in the late twenties, with only 10% of cases developing in the seventh decade. It is rare in childhood. There is not usually a family history of the disorder.

Clinical features

- Episodic cluster: The most common cluster variant; periods lasting 7 days to 1 year separated by pain-free remissions lasting 1–12 months.
- Chronic cluster: Unusual; attacks lasting more than 1 year without remission or remission lasting less than 4 weeks.

Headache features

- Excruciatingly severe unilateral orbital, supraorbital, temporal pain lasting 15 minutes–3 hours but usually 45–90 minutes.
- Attacks begin and end abruptly, have a tendency to occur at the same time of day, and may awaken the patient from sleep.
- Frequency may range from one every other day to eight per day.
- Associated autonomic features are conspicuous and include lacrimation, nasal congestion, rhinorrhea, facial/forehead sweating, miosis, ptosis, eyelid edema, and conjunctival injection. Concomitant gastrointestinal symptoms are unusual.
- Restlessness or agitation may occur during the headache, in contrast to paroxysmal hemicrania.
- A minority of patients have typical migrainous auras.
- The most common precipitants are alcohol, nitroglycerin, and exercise.

Differential diagnosis

- Causes such as tumors need exclusion by MRI; occasionally secondary cluster headache is seen in association with lesions of the cavernous sinus.
- Features helpful in differentiating cluster headache from migraine include the following:
  - Relatively short headache duration
  - Rapid onset and cessation
  - Periodicity (daily and annually)
  - Alcohol precipitates attack within 1 hour rather than hours as in migraine.

- Paroxysmal hemicrania is similar but more common in females, with briefer and more frequent attacks. It is exquisitely responsive to indomethacin.
- Other differential diagnoses include temporal arteritis, Tolosa-Hunt syndrome, sinusitis, and glaucoma.

Management

- Acute attacks
  - Abortive medication often unsuccessful because of acuity and short duration of attacks.
  - Subcutaneous sumatriptan 6 mg has a rapid effect and a high response rate. This may be used twice daily. Alternatives include sumatriptan 20 mg intranasally and zolmitriptan 5 mg orally.
  - 100% oxygen, 7–12 L/min should be used for 20 minutes via a non-rebreathing mask.
  - Topical lidocaine (20–60 mg) as a 4%–6% solution instilled intranasally may be a useful adjunct.

Preventive treatments

- Prophylactic therapy may include calcium channel blockers, valproic acid, topirimate, melatonin, corticosteroids, lithium, and capsaicin (Table 7.4). Methysergide may be useful in patients with clusters lasting a few weeks. Start at 1 mg/day, increasing the dose by 1 mg every 3 days to a tid regimen, with further dosage increases every 5 days to a maxiumum of 4 mg tid. Prolonged treatment is associated with retroperitoneal, cardiac, and pleural fibrosis. Therefore, a drug holiday for 1 month is required every 6 months.
- Ergotamine 1–2 mg po or rectally can be taken 1 hour prior to an attack or at bedtime if they occur predictably. Concomitant use of sumatriptan is contraindicated.

Nonmedical therapy

- If medical therapy fails, unilateral chronic cluster may be treated with ablation of the sensory input of the ipsilateral trigeminal nerve and autonomic pathways, with an overall success rate of approximately 75%. Gamma knife radiosurgery and deep brain (hypothalamic) stimulation are other surgical modalities that are under study.

Trigeminal neuralgia

This disorder is manifested by abrupt severe and repetitive lancinating pain within one or more divisions of the trigeminal nerve (most often the first and second divisions).

Epidemiology

- Annual prevalence is approximately 6/100,000; females are more often afflicted than males, and onset tends to be later in life, with onset in the sixth or seventh decade in >50% of cases.

Clinical features

- The neurological examination including facial sensation is normal, although frequent successive attacks may produce lingering pain. During some attacks, facial contortion may be seen: "tic doloreux"
- There tends to be a refractory period after an attack.
- Triggers include cutaneous sensory stimuli such as light touch, shaving, eating, talking, and drafts of cold air.
- Attacks during sleep are rare.
- Secondary weight loss, dehydration, and depression may occur.
- Secondary causes include the following:
  - Neoplasms of the 5th root entry zone such as schwannomas, meningiomas, and epidermoid cysts
  - Syringomyelia
  - Basilar ectasia/impression
  - Malignant/inflammatory infiltration of the skull base
  - Multiple sclerosis, particularly in younger patients with bilateral symptoms

A significant proportion of "idiopathic" cases are due to arterial or venous compression of the posterior 5th nerve root.

Differential diagnosis

- Temporomandibular joint disorder (TMJ) dysfunction
- Atypical migraine
- Atypical facial pain
- Pterygopalatine neuralgia
- Trigeminal autonomic cephalgias, e.g., cluster headche

Investigation

- MRI of the brain is usually indicated to exclude secondary causes. In younger patients it is particularly important to consider MS; 2%–8% of patients presenting with trigeminal neuralgia are also thought to have MS.

Management

Drug treatment

Medications should be initiated at low daily dosages and gradually titrated upward to clinical effect; see Table 7.4.

- Occasionally, combinations of drugs (e.g., baclofen and carbamazepine) may be used at lower dosages to avoid side effects associated with high doses of single agents
- In crises, consider intravenous phenytoin (as fosphenytoin 250 mg).

Surgical treatment

In cases refractory to medical therapy or those in whom there are intolerable side effects, surgical options (Table 7.5) need to be considered.

Table 7.4 Drug treatments for trigeminal neuralgia

Drug	Dose (mg/D)	Side effects
Carbamazepine	300–1000	Drowsiness, ataxia, hyponatremia, neutropenia, hepatic dysfunction, drug interactions
Oxcarbazepine	300–1200	Drowsiness, ataxia, hyponatremia
Baclofen	30–90	Sedation, drowsiness
Phenytoin	200–300	Sedation, ataxia, drug interactions
Gabapentin	300–3600	Sedation
Lamotrigine	100–400	Sedation, rash

Table 7.5 Surgical options in the treatment of trigeminal neuralgia

Procedure	Comments
Peripheral branch alcohol injection	Safe. Mild sensory loss.
Cryotherapy	High recurrence rate: mean, 10 months
Radiofrequency thermocoagulation	Safe. Risk of anesthesia dolorosa. Recurrence rate 60% at 5 years
Glycerol injection to Meckel's cave	Safe. Recurrance rate 65% at 5 years
Microvascular decompression via posterior fossa approach	Mortality up to 0.4% Complications: CSF rhinorrhea, cerebellar venous infarction. Recurrence rate 25% at 5 years
Gamma knife radiosurgery directed at the trigeminal nerve stereotactically	Long-term effects unknown. 6 months for effect. Low recurrence rate.

Idiopathic intracranial hypertension (IIH)

IIH is a syndrome of increased intracranial pressure without evidence of hydrocephalus or mass lesion. The composition of the CSF remains normal. This entity has previously been referred to as benign intracranial hypertension (BIH) or pseudotumor cerebri.

Epidemiology

- Occurs at a frequency of 1 case/100,000/year in the general population.
- There is a marked female preponderance.
- Age range: 15–44 years.

- Major risk factors:
  - Female sex
  - Obesity
  - Recent weight gain
  - Hypertension
  - Menstrual irregularity
- In any patient without risk factors, special care should be taken to exclude intracranial hypertension secondary to other causes.

Pathophysiology

The pathophysiology is not well understood. Possible mechanisms include the following:

- Obstruction to CSF outflow at the level of the arachnoid villi or in the draining veins, with some recent neuroimaging studies suggesting partial venous outflow obstructions in patients with IIH
- Excess CSF production
- Cerebral edema of unknown cause

Clinical presentation

Usual symptoms reflect increased ICP or papilledema:

- Daily headache (throbbing) associated with nausea and vomiting
- Visual symptoms: transient visual obscurations lasting a few seconds, visual blurring, and/or visual field loss
- No localizing neurological signs except uni- or bilateral VI nerve palsies causing diplopia
- Cases are reported with 3rd and 4th nerve palsies, internuclear ophthalmoplegia, and skew deviation. There are very atypical and other causes such as venous sinus thrombosis need to be excluded.
- Papilledema may occasionally be unilateral.
- Papilledema may be absent in patients with optic atrophy.
- Central visual loss occurring early should raise concern about some other cause of optic disc edema such as optic neuritis or anterior ischemic optic neuropathy.
- Central visual loss may occur in IIH if severe disc edema is associated with retinal edema, hemorhages, exudates, or choroidal folds in the papillomacular bundle or the macula.

Diagnosis of papilledema may be difficult. Clues that an apparently swollen disc is not due to papilledema:

- Blind spot is not enlarged
- Spontaneous venous pulsation may be present or venous pulsation will appear on minimal orbital pressure
- The absence of an optic cup in a mild to moderately swollen disc
- Abnormal vessels at the disc

An ophthalmological consultation will be helpful in cases where the diagnosis of papilledema is challenging.

Conditions that may produce intracranial hypertension and mimic IIH

Medical disorders

- Addison disease
- Hypoparathyroidism.
- Chronic obstructive pulmonary disease
- Right heart failure with pulmonary hypertension
- Sleep apnea
- Renal failure
- Severe iron deficiency

Medications

- Tetracyclines
- Vitamin A and related compounds
- Anabolic steroids
- Withdrawal of corticosteroids
- Growth hormone administration
- Nalidixic acid
- Lithium
- Norplant levonorgestrel implant system

Obstruction to venous drainage

- Cerebral venous thrombosis
- Jugular vein thrombosis

Imaging studies

- MRI and MR venography should be performed to exclude hydrocephalus, mass lesions, or meningeal infiltration. Isodense tumors and subdural collections may be missed by CT. MR venography will detect most venous sinus obstructions. If MRI is unavailable or not possible because of the patient's size, a CT with contrast should be performed.
- Radiographic signs of raised intracranial pressure in IIH include flattening of the posterior globe (80%) and an empty sella (70%). Slit-like ventricles are *not* a sign of IIH.

Lumbar puncture

- The lumbar puncture (LP) is done with the patient in the lateral decubitus position.
- Obesity may make it difficult to perform LPs on this group of patients. LPs can be done under fluoroscopic guidance, although the radiologist needs to be informed that an opening pressure is required with the patient positioned accordingly. Normal CSF pressure is less than 200 mm of water. The pressure increases with increasing weight.
- To diagnose IIH, CSF pressure >250 mm water. Levels between 200 and 250 mm CSF are nondiagnostic and need to be repeated. Occasionally, a transducer monitor via a lumbar drain may be needed to clarify the diagnosis.

Management

No evidence of visual loss

Conservative management with:

- Weight loss
  - Diuretics: Acetazolamide is the drug of choice as it reduces the rate of CSF production by the choroid plexus. The starting dose is 125 mg bid, increasing to 250 mg tid, and then as tolerated to 250 mg qid. Limiting side effects can include paresthesias, altered taste, and depression. Furosemide can sometimes be used as an alternative. Headache can be treated symptomatically with amitriptyline.
- Close follow-up is required with assessment of visual acuity, visual fields (automated or Goldmann), initially at 1 month, then every 3 months. Subsequent follow-up is dependent on the clinical course.

Evidence of visual loss

Surgical intervention needs to be considered. The options are as follows:

- Ventriculoperitoneal shunting. Side effects include infection, shunt obstruction, and low-pressure headache.
- Optic nerve sheath fenestration
- There are no data comparing the efficacy or morbidity of these two procedures.

Repeated LP

- May be unpleasant for the patient
- Can result in low-pressure headache, which complicates the clinical picture
- Helpful in some patients with severe headache and also in the management of IIH in pregnancy when acetazolamide and nortryptylline are relatively contraindicated.

Low-pressure headache

Epidemiology and causes

This disorder is most commonly the result of lumbar puncture, craniotomy, CSF shunt placement, or trauma. Occasionally it is the product of a spontaneous dural tear, and it can also be seen in the setting of dehydration, uremia, meningitis, or hypertonic saline administration. The true overall incidence of this condition is unknown; the risk of post-lumbar puncture headache is highest in younger, female patients.

Clinical features

- Onset following lumbar puncture varies from 15 minutes to 12 days. If untreated, the headache most commonly lasts 4 to 8 days and then resolves, although it may persist for months.

- Low-pressure headache is worst with the patient standing erect and consistently relieved by lying down. It may be exacerbated by movement of the head, coughing, and straining. Dizziness, nausea, vomiting, and tinnitus are associated symptoms, which tend to correlate with the severity of the headache.
- Neurological examination is usually unremarkable, although mild neck stiffness may be elicited.

Investigation

- Further investigation is usually unnecessary if the cause is known (i.e., recent lumbar puncture or shunt placement).
- If the cause is not apparent, a CT or MRI should be performed prior to lumbar puncture and cisternography. The MRI often reveals diffuse pachymeningeal enhancement, diminished ventricular size, and sometimes subdural collections and descent of the cerebellar tonsils.
- The CSF opening pressure may vary from 0 to 70 mmH_2O, although it is sometimes normal if the patient has been lying down prior to the LP.
- Radioisotope cisternography is used to identify occult CSF leaks, often the product of mild spinal or cranial nerve root avulsion.

Treatment

- Noninvasive therapy is often effective, and it includes oral or intravenous caffeine therapy, followed by a brief trial of corticosteroids if the headache is refractory.
- If noninvasive therapy is unsuccessful, placement of an epidural blood patch should be attempted. Recurrences can be treated with repeat blood patch placement or epidural saline infusion.

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Chapter 8

Dementias

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Diana Gomez-Hassan, MD, PhD

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Dementia: introduction

Dementia is defined as a syndrome of progressive impairment—in the absence of delirium—in two or more areas of cognition sufficient to interfere with work, social function, or relationships. The areas of cognition included in the definition are as follows:

- Memory
- Language
- Abstract thinking
- Praxis
- Visuospatial or perceptual skills
- Personality
- Social behavior

Epidemiology

At 60 years of age, 1% of the population is affected; 40% of those >85 years. High levels of education may be protective against early cognitive decline in setting of typical pathology but not against development of pathology itself.

Etiology

Common

- Alzheimer disease (60%–80%)
- Dementia with Lewy bodies/Parkinson disease with dementia (10%–20%)
- Frontotemporal dementia (5%–10%)
- Cerebrovascular disease (10%–20%)

Rarer causes

- Corticobasal degeneration
- CJD
- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

Treatable causes (<1% of dementias)

- Depressive pseudodementia
- Normal pressure hydrocephalus
- B_{12} deficiency
- Hypothyroidism
- Infection, e.g., syphilis, HIV
- Benign tumors, e.g., subfrontal meningioma
- Subdural hematoma
- Subclinical seizures impacting memory, attention, and concentration
- Sleep disorders (e.g., obstructive sleep apnea) leading to pseudodementia

Investigations

First line

- CBC-PD
- Comprehensive metabolic panel
- Thyroid studies (TSH and free T4)
- B_{12}
- CT or (preferred) MRI
- Dementia screening examination such as mini-mental status examination (MMSE; see Appendix).

Second line (directed by clinical suspicion)

- ESR
- CSF examination
- HIV, RPR, VDRL
- ANA
- Lab screening for inherited metabolic deficiencies
- Formal neuropsychological assessment
- Genetic testing
- EEG
- PSG
- Volumetric MRI
- SPECT
- Brain biopsy

Alzheimer disease (AD)

Epidemiology

- Incidence: 1.2 per 1000 person years among 65–69-years olds, increasing to 53.5 in those >90 years.
- Prevalence 4.4% in those >65 years
- Affects females more than males
- Most common >65 years
- Sporadic (common) and familial (rare) forms—no specific features to distinguish sporadic from familial apart from early onset

Pathology

Deposits of amyloid protein in cortex with neuritic plaques (Fig. 8.1). Neurofibrillary tangles contain tau and ubiquitin proteins. In cases of amyloid angiopathy, amyloid is found in vessel walls.

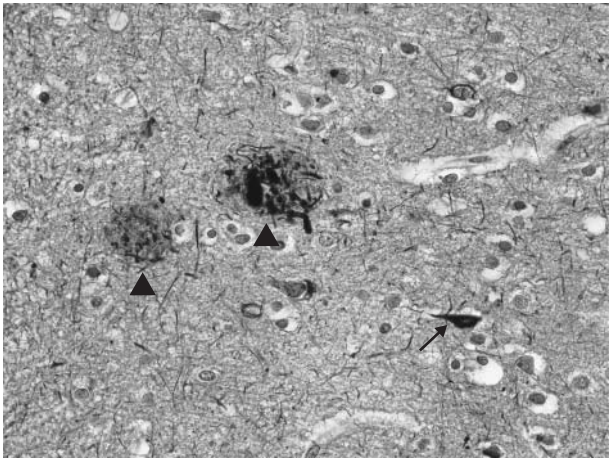

Figure 8.1 Temporal lobe pathology from patient with AD. Neurofibrillary tangles (black arrow) represent degenerating neurons with abnormal tau and ubiquitin deposition. Amyloid plaques (black arrowhead) represent sites of extracellular amyloid deposition and often contain dystrophic neurites. Mature plaques have a dense core and surrounding "halo." (Photo courtesy of Mila Blaivas, University of Michigan Pathology Department.)

Genetics

Familial cases (<5% of AD) tend to present at a younger age. Familial autosomal dominant cases associated with mutations in three known genes:

- APP gene (amyloid precursor protein) on chromosome 21
- Presenilin 1 (~50% of early-onset AD) on chromosome 14
- Presenilin 2 on chromosome 1

Other familial cases without characterized mutations as yet.

Risk factors

- Increasing age
- Apolipoprotein E ∈4 allele
  - Having 1 ∈4 allele confers risk and having 2 ∈4 alleles confers even greater risk.
  - About 50% of subjects in the sporadic AD population have an ∈4 mutation.
- History of AD in one or two first-degree relatives
- Head injury with loss of consciousness >30 minutes

Clinical features

- Memory impairment. Episodic (personal experiences) and semantic (store of conceptual and factual knowledge) are affected. Complaints of forgetting day-to-day events, learning new information. Impairment for recent past > distant past.
- Visuospatial impairment, e.g., getting lost when driving
- Constructional and dressing apraxia
- Language impairment, e.g., word-finding difficulties. Alexia, agraphia, acalculia
- Mini-mental state examination (MMSE). A practical screening examination. See Appendix
- Physical signs:
  - Mild akinetic rigid syndrome
  - Myoclonus

Investigations

- EEG: mild slowing in moderate disease; nonspecific
- MRI to exclude treatable causes, e.g., hydrocephalus. See Figure 8.2.
- Hippocampal volume measurements show correlation with histology. Can be used to monitor disease progression:
  - Bilateral hippocampal/entorhinal cortex volume loss disproportionate to atrophy
  - Volume loss with posteroanterior gradient
  - Small-vessel white matter hyperintensities on T2W common
- SPECT: bilateral temporal/parietal perfusion/metabolism defects

Management

- Multidisciplinary team with nurse, counselor, and psychiatrist.
- Ten to fifteen percent risk per year of progression to AD. Treatment with acetylcholinesterase inhibitors (AChI) provides mild symptomatic benefit but does not modify disease progression rate.
- AChI and memantine (NMDA receptor antagonist) may improve cognition and neuropsychiatric symptoms for up to several years. Response is variable on an individual basis. If no benefit from one drug, switch. Stop if MMSE <12; however, restart if significant worsening of behaviors/abilities on discontinuation
  - Donepezil, 5–10 mg daily
  - Rivastigmine, 1.5–6 mg bid
  - Galantamine, 4–12 mg bid
  - Memantine, 5–10 mg bid
- Behavioral and psychiatric disorders are common. Consider (initial doses):
  - Quetiapine, 25 mg daily
  - Olanzapine, 2.5 mg daily
  - Risperidone, 0.5 mg daily

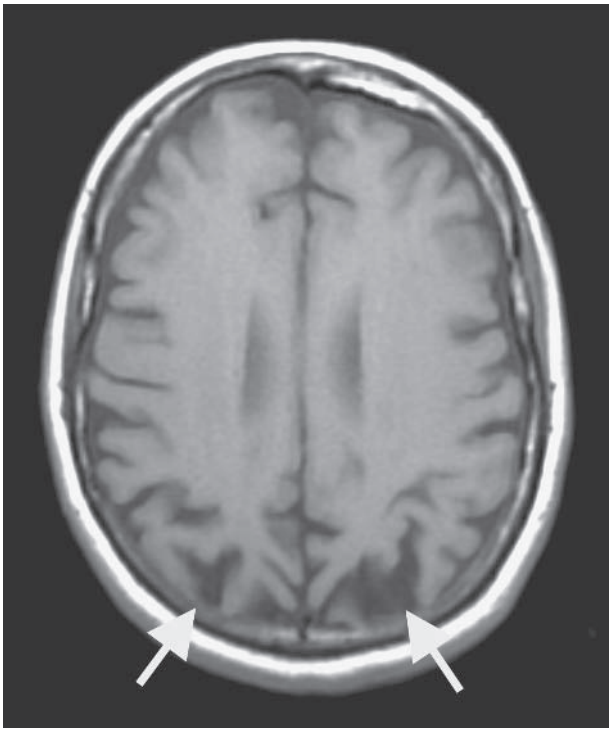

Figure 8.2 MRI of AD. Axial T1 weighted image demonstrates disproportionate volume loss in the biparietal regions in a patient with clinical evidence and concordant PET imaging of AD.

Dementia with Lewy bodies (DLB)

Dementia with Lewy bodies is a combination of dementia and parkinsonism. Dementia precedes parkinsonian features by >1 year. See Box 8.1.

Epidemiology

- Usually sporadic, but familial cases occur (with younger presentation of disease). Most commonly elderly patients (mean age of presentation: 75 years). Males outnumber females.

Box 8.1 PDD vs DLB: continuum or discrete diseases?

PDD and DLB may be variant presentations of the same disease. The symptoms and pathology are essentially the same; the definitions may be arbitrary:

- DLB: dementia is prominent initially with mild symptoms of or later development (>1 yr) of dopa-responsive Parkinsonism.
- PDD: Dopa-responsive parkinsonism develops at least 1 year prior to symptoms of dementia. Incidence of dementia in a patient with PD is 7% per year; cumulative risk of dementia by age 85 is 65%.

Alternatively, PDD and DLB may represent separate neurodegenerative diseases

- DLB: prominent and early cortical involvement with Lewy body pathology; rapid cognitive decline, lesser response to L-dopa
- PDD: Predictable spread of Lewy body pathology starting in brainstem and olfactory tracts—cortical involvement a late development; slower progression of dementia, ongoing clear response to L-dopa.

Note: Sleep disorders, particularly REM behavior disorder (RBD) are common in both disorders and often present many years prior to symptoms of Parkinsonism or dementia.

Pathology

- Generalized brain atrophy, depigmentation (loss of dopamine-producing cells) of substantia nigra. Lewy body inclusions in cortical neurons. Lewy neurites are degenerating neurons that stain for alpha-synuclein and ubiquitin. Forty percent of cases have amyloid deposits. Neurofibrillary tangles are rare or absent.

Clinical features

- L-dopa responsive parkinsonism
- Cortical symptoms—aphasia, apraxia
- Fluctuating mental state
- Visual hallucinations and illusions
- Neuroleptic sensitivity
- Dysautonomia
- Sleep disorders

Investigations

- MRI: generalized atrophy
- Absence of significant temporal atrophy in a demented patient suggests DLB.

Parkinson disease with dementia (PDD)

PDD is a combination of parkinsonism and dementia. Parkinsonian features precede onset of dementia by >1 year. See Box 8.1.

Epidemiology

- Prevalence of dementia in PD population 30%–40% in community-based studies
- Likelihood of dementia correlated with older age, duration, and severity of Parkinsonism

Pathology

- Presence of Lewy bodies and Lewy neurites containing alpha-synuclein and ubiquitin prominently in substantia nigra but also in cortex. Loss of dopaminergic neurons (Fig. 8.3)

Clinical features

- L-dopa-responsive parkinsonism
- Visual hallucinations and illusions
- Bradyphrenia
- Dysautonomia
- Sleep disorders
- MCI and dementia presenting late in the course characterized by visiospatial, memory, and language impairment.

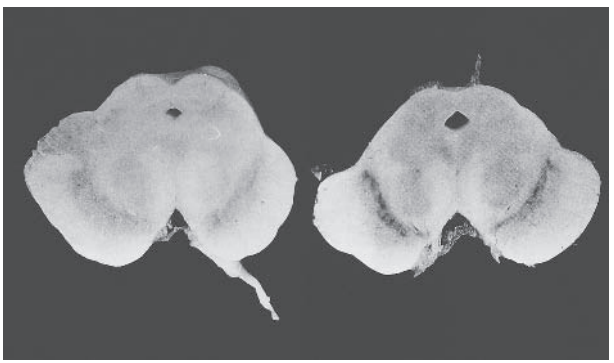

Figure 8.3 Depigmented substantia nigra in PD (left) compared with a normal midbrain (right).

Parkinsonian syndromes associated with dementia

Patients have parkinsonian features of bradykinesia, bradyphrenia, and postural instability. They may be atypical in symmetrical presentation of symptoms, lack or tremor, or variation in posture (e.g., retroflexed neck instead of stooped posture). The diagnostic clues are the features not seen in PD.

Progressive supranuclear palsy With gaze palsy, usually upgaze or downgaze, corrected or improved with the oculocephalic maneuver, retroflexed neck, backward falls, mild dementia.

Corticobasal ganglionic degeneration "Alien" limb phenomenon: progressive clumsiness and inability to control a limb.

Multiple system atrophy Autonomic dysfunction with or without preceding cerebellar ataxia, variable atrophy of olives, pons, or cerebellum. Dementia is mild or absent in most patients.

Vascular dementia

Epidemiology

- Usually >40 years. Risk factors include hypertension, smoking, and vascular disease.

Pathology

- Multiple infarcts in cortical and subcortical areas or fibrous and hyaline degeneration of small arteries leading to white matter infarction.

Clinical features

- Recurrent stepwise deterioration
- Pyramidal signs
- Pseudobulbar palsy
- When mainly subcortical disease slowly progressive syndrome with dysarthria, parkinsonism, gait disorder (marche á petits pas) = subcortical arteriosclerotic dementia.

Investigations

MRI: areas of typical infarction (Fig. 8.4). In subcortical dementia widespread leukoariosis, mainly anterior and periventricular.

Figure 8.4 MRI of vascular dementia. Axial flair weighted image demonstrates patchy and confluent hyperintense areas within the cerebral white matter and diffuse volume loss in a patient with dementia.

Frontotemporal dementia

Epidemiology

- Usual onset 45–65 years
- M = F

Pathology

Atrophy affecting frontal and anterior temporal lobes (Fig. 8.5). In progressive nonfluent aphasia, asymmetrical atrophy of the dominant hemisphere.

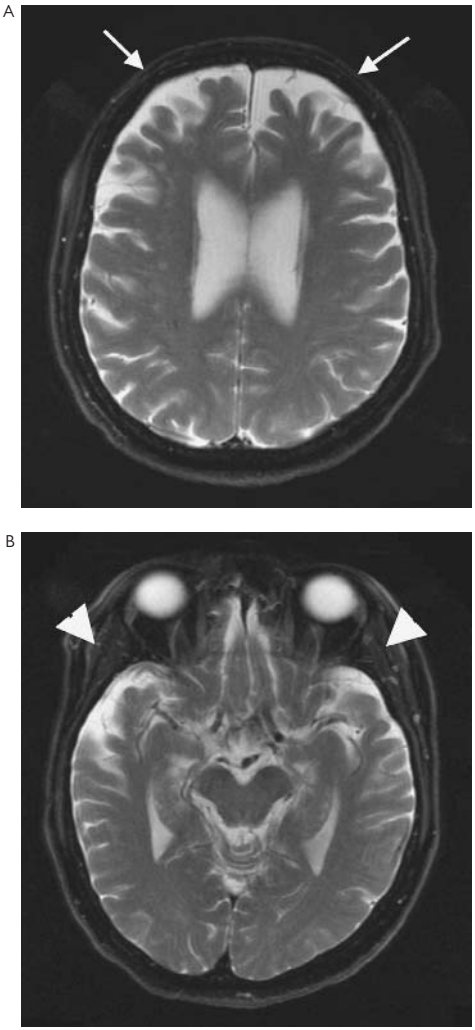

Figure 8.5 MRI of frontotemporal dementia. Axial T2 weighted images through the frontal (A) and temporal lobes (B) demonstrates disproportionately greater atrophy in the frontal (arrows, A) and temporal (arrowheads, B) lobes in a patient with clinical features of frontotemporal dementia.

Bilateral atrophy of the temporal lobes is found in semantic dementia form. Variable histopathology—cortical loss of pyramidal cells, sometimes with inclusion of (Pick) bodies and swollen (Pick) neurons (Fig. 8.6).

Genetics

Fifty percent autosomal dominant inheritance. Some with parkinsonian features have tau mutations on chromosome 17q21. Associated cases with motor neuron disease link to chromosome 9.

Clinical features

Frontotemporal dementia

- Change in personality, social and personal behavior
- Apathetic, emotionally blunted
- Overactive, disinhibited
- Stereotypic movements, e.g., hand rubbing
- Perseveration
- Loss of insight
- Memory intact

Investigations

- EEG: normal
- MRI: frontal and anterior temporal lobe atrophy

Progressive nonfluent aphasia

- Pure language deficit
- Nonfluent, effortful speech
- Loss of prosody
- Repetition impaired
- Impairment of well-rehearsed series, e.g., days of the week
- Anomia
- Writing affected
- Comprehension intact

Note: Alzheimer patients may develop a similar language disorder in association with abnormalities in other domains.

Semantic dementia

- Loss of meaning of words
- Inability to recognize objects and faces
- Speech is fluent, effortless, but lacks content
- Semantic paraphasias, e.g., dog for cat
- Anomia
- Impaired comprehension

Note: May be confused with AD but memory for day-to-day events and autobiographical details is intact.

Frontotemporal dementia with MND

Development of amyotrophic lateral sclerosis form of MND after onset of dementia.

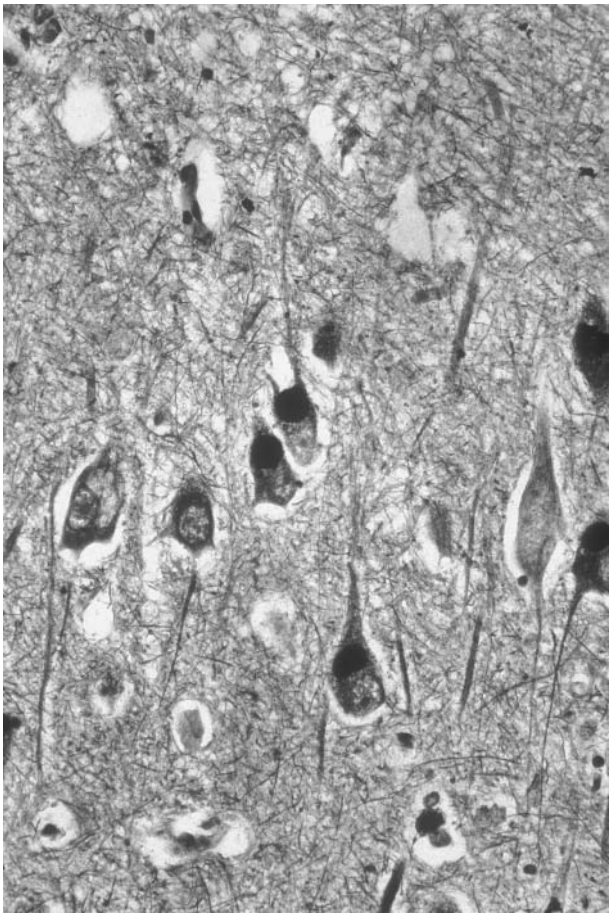

Figure 8.6 Pick disease: Pick cell within the cortex exhibits ballooned achromatic cytoplasm. (Courtesy of Mila Blaivas, Department of Pathology, University of Michigan.)

Other dementias

CADASIL

Clinical features

- Stroke-like episodes
- Cognitive impairment in variable cognitive domains
- Strongly associated with migraine

Investigations

- MRI: extensive white matter T2W signal change involving the temporal lobes especially anteriorly, and the subinsular region
- Genetics: Notch 3 mutation on chromosome 19

Huntington disease

- Autosomal dominant, highly penetrant, chr. 4, huntingtin protein (function unknown)
- Trinucleotide (CAG) repeat disorder: number of repeats correlated with age of onset of symptoms
- Hyperkinetic movements manifest initially
- Degree of impairment of memory and executive function correlated with degree of hypometabolism in striatum and bilateral frontotemporal areas (with occipito-temporal metabolism reduced late in disease)
- MRI imaging: progressive atrophy of caudate and putamen

Prion diseases

Normal PrP coded by gene on chromosome 20

Sporadic CJD

- Most common form of CJD (incidence of 0.5–1.5 per million persons per year)
- No specific mutation in PrP gene; however, most individuals are homozygous at codon 129 for methionine or valine
- Rapidly progressive dementia over weeks to months
- Myoclonus
- Atypical symptoms may include cerebellar ataxia, cortical blindness, or amyotrophy
- 14–3-3 protein present in CSF
- EEG: periodic sharp waves
- MRI: signal changes in basal ganglia
- Death within 6–12 months from presentation

Familial CJD

- Most common point mutation at codon 20
- Earlier onset than sporadic CJD
- Otherwise indistinguishable from sporadic CJD

Gerstmann–Straussler–Scheinker syndrome
- Point mutation codon 102
- Onset in third or fourth decades
- Cerebellar features
- Dementia
- Progressive over years

Fatal familial insomnia
- Onset at 20–70 years
- Progressive insomnia
- Autonomic features
- Memory impairment

HIV dementia complex
- Associated with HIV-1 infection
- Memory loss, apathy, and cognitive slowing
- MRI: frontotemporal atrophy
- PET scan: subcortical hypermetabolism in early stages
- Pathology: multinucleated giant cells, microglial nodules, perivascular infiltrates
- Imperative to rule out treatable conditions that can impact cognition such as:
  - Cryptococcus, CMV, PML, toxoplasmosis, lymphoma, neurosyphilis, tuberculosis

Metabolic disorders
A number of inherited metabolic disorders may be associated with dementia, either rarely or in later stages. These might include the following:
- Leukodystrophies: adrenoluekodystrophy, metachromatic leukodystrophy, Krabbe disease
- Storage diseases: GM1 and GM2 gangliosidoses, Gaucher syndrome, Niemann-Pick disease, mucopolysacchraidoses
- Mitochondrial diseases: MERFF and MELAS
- Wilson disease
- Cerebrotendinous xanthomatosis
- Kufs disease
- Membranous lipodystrophy

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Chapter 9

Movement disorders and ataxia

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Movement disorders: introduction

Movement disorders are broadly categorized by either an excess or a paucity of movement—on a nonvolitional basis—into hyperkinetic and hypokinetic movement disorders, respectively. Regardless of the genetic or environmental influences underlying the movement disorder, the common underlying etiology is usually an abnormality of the basal ganglia and their connections.

The basal ganglia consist of deep nuclei with input from the cerebral cortex through the thalamus and output to the thalamus/cerebral cortex and pyramidal system. Within the basal ganglia are complex inhibitory and excitatory connections allowing precise control over initiation and fine control of movements. (See Fig. 9.1.)

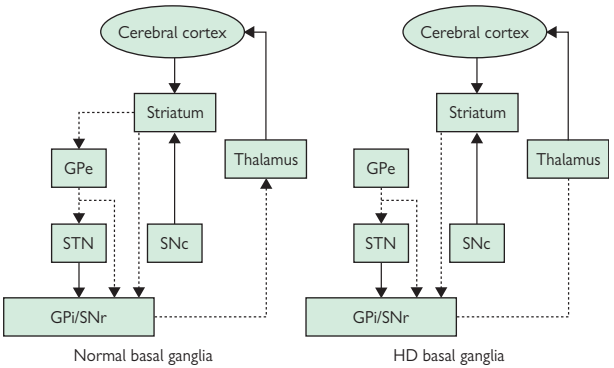

Figure 9.1 Basal ganglia pathways. The plain and dotted lines indicate excitatory and inhibitory pathways, respectively. Damage within the pathways may unbalance the system, leading to hyperkinetic or hypokinetic movement disorders. Striatum is comprised of caudate and putamen. GPe, globus pallidus external segment; GPi, globus pallisus internal segment; STN, subthalamic nucleus; SNr, substantia nigra pars reticulate; SNc, substantia nigra pars compacta. (From Bates G, Harper P, Jones L [Eds.] [2002]. *Huntington's Disease*. Oxford, England: Oxford University Press. Used with permission of Oxford University Press.)

Hypokinetic movement disorders

Hypokinetic movement disorders are characterized by rigidity and bradykinesia or akinesia. Postural instability and gait disorder may be present. Parkinson disease is the most common hypokinetic disorder; parkinsonism may be seen in a smaller number of other hereditary, sporadic, and acquired disorders. Parkinson disease is the prototypical hypokinetic movement disorder.

Parkinsonism and Parkinson disease (PD): introduction

Causes of parkinsonism

- Idiopathic PD
- Familial (hereditary) PD
- Parkinsonian syndromes:
  - PSP
  - MSA
  - Corticobasal degeneration (CBD)
- Secondary parkinsonism:
  - Vascular
  - Drug induced
  - Postencephalitic
  - Hydrocephalus
- Degenerative disorders with associated parkinsonism:
  - Alzheimer disease (AD)
  - Parkinson—dementia—motor neuron disease complex
- Genetic disorders with associated parkinsonism:
  - Wilson disease (consider in all cases <50 years)
  - Huntington disease (HD)(akinetic rigid [Westphal] variant)
  - Dopa-responsive dystonia

Epidemiology of PD

- Prevalence: 100–200/100,000
- In United States, 1,000,000 cases at any one time
- M:F ratio: 1.35:1
- Uncommon in persons under 40 years
- Increases in population after age 60; mean age at diagnosis 70.5 years

Etiology of PD

Idiopathic PD

- Increased risk of PD:
  - Pesticides
  - Exposure to manganese

  - Rural residence, farming
  - MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)—initially synthesized and used as an illegal street drug
- Decreased risk has been associated with cigarette smoking and caffeine intake.

Familial PD

- Rare (often one family per mutation); multiple genotypes impacting different proteins (or unknown products) with widely different function resulting in similar phenotypes
- Ten or more mutations identified (e.g., PARK 1–10) on 5 or more chromosomes
- Autosomal dominant and recessive forms
- Parkinsonian features at young age, though may present late occasionally

Pathophysiology of PD

- Hallmarks of PD are the presence of Lewy bodies + neuronal cell death in the pars compacta of the substantia nigra.
- PD does not develop until striatal dopamine (DA) levels drop to 20% and substantia nigra (SN) cell loss exceeds 50%.
- Functional anatomy involved in PD includes:
  - Primary motor cortex
  - Supplementary motor area
  - Striatum (putamen and caudate)
  - Globus pallidus
  - Substantia nigra (SN)
  - Subthalamic nucleus (STN)
  - Thalamus
- SN acts like an accelerator on the basal ganglia and damage results in slowing.
- STN is a brake and damage therefore causes excessive movement.

Clinical features of parkinsonism and PD

Diagnosis of a parkinsonian syndrome

Bradykinesia: slowness of initiation of voluntary movement with progressive reduction in speed and amplitude with repetition, e.g., thumb and index finger tapping. Plus at least one of the following:

- Rigidity: increased tone; cogwheeling (a "catching" or ratcheting felt by examiner when joints passively manipulated)
- Rest tremor:
  - May be the first symptom in 75% of cases of PD.
  - Twenty percent of patients never develop tremor.
  - Some patients may in addition have a postural element to the tremor—this is delayed in onset ("reemergent"), comes on a short period after the posture is adopted.

- Postural instability is not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Features supportive of PD: ≥3 for definite PD

- Unilateral onset
- Rest tremor
- Progressive
- Persistent asymmetry affecting the side of onset most
- Good response to L-dopa
- Severe L-dopa-induced chorea
- L-dopa response for >25 years
- Clinical course >10 years

Exclusion criteria for PD

- History of repeated strokes with stepwise progression of parkinsonian features (vascular PD)
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy (PSP)
- Cerebellar signs (MSA).
- Early severe autonomic involvement (MSA)
- Early severe dementia (Lewy body dementia)
- Babinski sign (but note striatal toe may mimic)
- Negative response to L-dopa (if malabsorption excluded)
- MPTP exposure

Other features of PD

- Constipation: often the earliest symptom, beginning 1–2 decades in advance of other symptoms
- Anosmia: 80% PD patients have decreased sense of smell. If normal consider PSP, CBD, or MSA.
- Dystonia:
  - Unusual in early disease—consider MSA
  - More common after L-dopa therapy
- Bladder and bowel symptoms:
  - Mild urinary symptoms. Frequency, urgency, but rarely incontinence may occur due to detrusor hyperreflexia.
  - In MSA these occur earlier and are more severe.
  - Constipation is common.
- Postural hypotension: mild but may be exacerbated by levodopa and dopamine agonists.
- Speech disorder:
  - Hypophonia (monotonous and low volume)
  - Tendency to repeat the first syllable (pallilalia)

- Sleep disorders:
  - Restless legs syndrome
  - REM sleep behavior disorder where patients act out their dreams—may precede other symptoms and diagnosis by a decade or more
- Dementia. In the late stage, 20% of patients may have dementia:
  - With memory impairment
  - Fluctuating confusion
  - Visual hallucinations
  - Dopaminergic medication may compound the problem.

Differential diagnosis of PD and investigation

Differential diagnosis

- Parkinsonian syndromes
  - For differential diagnoses, see Table 9.1.
- Essential tremor (ET) versus PD
  - ET 10 times more prevalent than PD.
  - ET is a postural ± action tremor. A severe postural tremor may be present at rest but is not "pill rolling."
  - Patients with ET may also have vocal tremor; head tremor ("no–no" or "yes–yes").
  - In PD there may be jaw tremor; leg rest tremor.

Investigations

- No diagnostic test for PD. Diagnosis is made on clinical grounds.
- 123I-FP-CIT SPECT scan (DaTscan). Ligand binds to the dopamine reuptake transporter protein in the presynaptic terminals. Decrease indicates loss of striatonigral neurons. Useful in differentiating ET from PD, but not PD from MSA and PSP.
- Exclude Wilson disease if onset <50 years:
  - Serum copper, ceruloplasmin
  - 24-hour urinary copper
  - Slit lamp examination for Kaiser–Fleischer rings
- MSA patients may have degeneration of Onuf nucleus—detected as polyphasic potentials with increased latency on urethral or sphincter EMG. Not routinely done for diagnosis.
  - False positives occur in patients who have had prostatic surgery and in occasional patients with PSP.
  - Sphincter EMG has a sensitivity of 0.74 and a specificity of 0.89.
- Autonomic function tests, if MSA is in differential. Similarly, a cognitive assessment: dementia is unusual in MSA.
- MRI (see Table 9.2).

Table 9.1 Features of other parkinsonian syndromes

Diagnosis	Clinical features	Response to levodopa
Multiple system atrophy (striatonigral degeneration, sporadic olivoponto-cerebellar atrophy, and Shy–Drager syndrome)	Early dysautonomia (orthostatic hypotension, impotence, bladder dysfunction), Cerebellar dysfunction Pyramidal signs, Stimulus-sensitive myoclonus Extreme forward flexion of neck (antecollis), Mottled cold hands Inspiratory stridor, Dysarthria	Good response in 20% and sustained in 13%. Dyskinesias or motor fluctuations may occur. Cranial dystonia prominent. Early wheelchair requirement due to early loss of postural reflexes and ataxia
Progressive supranuclear palsy	Supranuclear vertical gaze palsy Apraxia of eyelid opening, Axial rigidity > limb rigidity Early falls, Speech and swallowing disturbance Neck extension	Good response rare
Corticobasal degeneration	Apraxia, cortical sensory changes, alien limb behavior Pronounced asymmetric rigidity Limb dystonia Stimulus-sensitive myoclonus	None
Vascular parkinsonism	"Lower half" parkinsonism with prominent gait problems Minimal upper-limb dysfunction Pseudobulbar palsy Pyramidal signs	Minimal
Dementia with Lewy bodies	Early dementia Rigidity > bradykinesia or tremor Hallucinations Fluctuating cognitive status Exquisite sensitivity to neuroleptics	Motor features respond well. Psychiatric side effects

Table 9.2 MRI findings in parkinsonian syndromes

Syndrome	Finding
PD	Nigral patchy signal loss
MSA	Putamen: decreased lateral putamen signal on T2-weighted images due to iron deposition; increased signal lateral putamen due to gliosis. Pons: "hot cross bun" sign due to lateral and longitudinal fibers becoming evident on T2-weighted images. See Fig. 9.2.
PSP	Midbrain atrophy and 3rd ventricular dilatation
CBD	Asymmetrical atrophy

Drug-induced parkinsonism

- Depletion of presynaptic dopamine stores:
  - Reserpine
  - Tetrabenazine
- Dopaminergic blockers:
  - Neuroleptic drugs: phenothiazines (chlorpromazine), butyrophenones (haloperidol), thioxanthines (flupenthixol), and substituted benzamides (sulpiride)
  - Prochlorperazine prescribed for labyrinthine symptoms and nausea
  - Metoclopramide for GI symptoms

Clinical features

- Tremor and asymmetry as in PD
- Patients may have a mixed movement disorder with untreated parkinsonism coexisting with:
  - Orofacial dyskinesia
  - Stereotypies
  - Akathisia
- Parkinsonism may resolve within days of drug being stopped but may take years, especially if depot preparations have been used.
- Elderly patients may be left with residual signs.

Medical management of PD

Levodopa

Levodopa therapy remains the gold standard of treatment.

- Starting dose is Sinemet® (levodopa/carbidopa) 25/100 with meals tid.
- Side effects: nausea, vomiting, anorexia—often resolve spontaneously. Consider domperidone, 10–30 mg tid, to treat GI symptoms.
- Modified release preparations (Sinemet® CR) have no beneficial effect in the prevention of motor complications; however, they are especially useful for nocturnal hypokinesia and rigidity.
- Bioavailablity of the CR preparation is 70% that of the immediate release preparations.
- Dispersible levodopa preparation useful adjunct in kick-starting immediately on wakening or in the case of sudden "offs" or during episodes of nonresponsiveness.
- Motor complications develop in 50% of all PD patients after 6 years of levodopa therapy.
- Monotherapy with DA drugs is not associated with these complications; hence the rationale for delaying the use of levodopa therapies in younger patients if possible.

Long-term complications of levodopa therapy

- Involuntary movements or dyskinesias:
  - Peak dose choreathetoid dyskinesia
  - Diphasic dyskinesia
  - Dystonia (painful cramp)
- Response fluctuations:
  - End of dose deterioration (wearing off)
  - Unpredictable on/off switching
- Psychiatric:
  - Confusion
  - Visual hallucinations
  - Delusions
  - Illusions

Dopamine agonists (DAs)

- DA drugs (Table 9.3) act directly on postsynaptic dopamine receptors without the need for conversion to dopamine.
- DAs have a role as an alternative to levodopa as monotherapy, particularly in younger patients, to delay the use of levodopa and its long-term motor complications.
- In patients already on levodopa who have developed motor complications, DAs may be used with a consequent lowering of levodopa dosage.

Adverse effects

- All DAs: nausea, vomiting, postural hypotension, confusion, hallucinations, somnolence
- Domperidone, 10–20 mg tid is useful for the GI side effects and postural hypotension (peripheral effects).
- Ergot-derived DAs: ankle edema, erythromelalgia, Raynaud, retroperitoneal fibrosis, pleural effusions, cardiac valvular disease

Apomorphine

- Apomorphine, a potent D1 and D2 agonist, has poor oral bioavailability.
- Given by subcutaneous (SC) injection or continuous infusion.

Table 9.3 Dopamine agonists

Drug	Dosage
Ergot-derived	
Pergolide	3–5 mg/day
Cabergoline*	2–6 mg/day
Non–ergot-derived	
Ropinirole	Up to 24 mg/day in 3 divided doses
Pramipexole	Up to 3.3 mg/day in 3 divided doses

*Long half-life; once daily dose.

Indications

- SC injection of apomorphine may be used in assessing the dopaminergic response, pattern, and distribution of dyskinesias in patients on long-term levodopa therapy.
- Intermittent injections are used as rescue for severe "off " periods in patients already on maximal levodopa and DA therapy. Helpful in painful "off " period dystonias as well "off" period sphincter and swallowing difficulty.
- Continuous infusion: consider in all patients with refractory motor fluctuations that cannot be managed on oral therapy and require >6 apomorphine SC injections. This form of treatment should be considered prior to surgery.
- Temporary apomorphine therapy can be considered in PD patients undergoing abdominal surgery.

Apomorphine challenge test to assess effect

- Start domperidone 30 mg tid 36 hours prior to test.
- No oral anti-parkinsonian drugs for 4–6 hours before challenge
- Normal breakfast
- Assess baseline motor function with motor examination subscale (Section III) of the Unified Parkinson's Disease Rating Scale (UPDRS). See Appendix.
- Time to rise from a chair and walk 12 meters is measured.
- Apomorphine 1.5 mg SC administered and motor response observed for 30 minutes.
- Yawning may precede motor response.
- If no significant response, 3 mg is administered.
- Dose increased every 30 minutes up to 7–10 mg.
- Positive response is if there is an improvement in UPDRS score of 15%–20% or 25% increase in walking time

Other therapies

Anticholinergic agents

- Limited role and should only be prescribed in young patients with severe tremor and dystonia
- Trihexyphenidyl (benzhexol) (2–5 mg tid) is most commonly used.
- Side effects are a major drawback especially in elderly patients—confusion, cognitive impairment, nausea, dry mouth, precipitation of closed angle glaucoma, and urinary retention.

Amantadine

- Previously used in early PD to delay the use of levodopa; with the advent of DA drugs there is little use for this indication.
- New role in the management of drug-related dyskinesias due to glutamate antagonistic properties.
- Dose 100–300 mg/day.
- Side effects: confusion, hallucinations, ankle edema, livedo reticularis, insomnia (second dose at midday)

Selegiline

- MAOI drug has a mild symptomatic effect.
- Used as adjunct therapy to levodopa
- Dose of 5 mg bd
- Side effects: confusion, hallucinations, insomnia (second dose at midday)
- New melt preparation a given at a lower dose of 1.25–2.5 mg/day

COMT inhibitors

- Increase the amount of levodopa reaching CNS
- Entacapone (200 mg) prescribed with each dose of levodopa (dose range 400–1200 mg/day).
- Side effects: excess dopaminergic effects, dyskinesias managed by decreased levodopa, diarrhea

Surgical treatment of PD

New surgical procedures have developed as a result of a better understanding of the pathophysiology of PD (Table 9.4).

Table 9.4 Functional neurosurgery in PD

			Bilateral stimulation		
Outcome	**Postero ventral pallidotomy**	**Thalamotomy (VIM nucleus)**	**Thalamic (VIM nucleus)**	**STN**	**Pallidal**
Dyskinesias	++*	0	0	++	++
Tremor	+*	+*	+++	+	+
"Off" periods	+++	?	0	+++	+++
ADL	++	?	0	+++	+++
Medication	Increased	Unchanged	Unchanged	Reduced(++)	Reduced(+)
Morbidity (%)	5	5	5	?	?
Mortality (%)	2	?	0	?	?

+/++/+++ = increasing benefit. 0 = no benefit.

*Contralateral.

Management of other problems in PD

Depression

- Affects the quality of life in 40%
- Although SSRIs (e.g., citalopram and sertraline) are first choice, there is a concern this class of drugs may cause a deterioration of parkinsonian symptoms.
- Mirtazapine (presynaptic A_2 antagonist)
- Alternative drugs are the tricyclic antidepressants.
- In severe cases electroconvulsive therapy may be an option.

Psychosis

- Occurs in 10%–15%
- Symptoms: mild illusions, visual hallucinations, and paranoid delusions
- Underlying pathophysiology is combination of development of cortical Lewy body dementia and medication effects.

Management

- Treat any infection (urinary tract infections, bed sores, etc.).
- Correct any metabolic derangement, e.g., dehydration.
- Reduce and withdraw anticholinergics, selegiline, amantadine, DAs, and, lastly, levodopa.
- If necessary, balance between "mad and mobile" and "stiff but sane."
- Consider addition of a newer generation of antipsychotic drugs, e.g., quetiapine 25–50 mg daily to bid. Low-dose clozapine (6.25–50 mg, mean 25 mg) has been shown to be effective. Agranulocytosis occurs in 1.2% of patients using clozapine.

Dementia

- Features of Lewy body dementia include visual hallucinations, a fluctuating course with lucid intervals, and an exquisite sensitivity to neuroleptic drugs.
- Benefit with the use of cholinesterase inhibitor drugs used in the treatment of AD, such as donepezil and rivastigmine.

Sleep disturbance

Common problem due to combination of factors:

- Stiffness and rigidity, making it difficult to turn in bed. Consider CR levodopa preparations or cabergoline.
- Bladder disturbance due to detrusor hyperreflexia resulting in nocturia. Oxybutynin and tolterodine may help.
- Restless legs: CR levodopa or cabergoline at night
- Rapid eye movement (REM) sleep behavior disorder (RBD) where purposeful nocturnal motor activity occurs during REM sleep phase. Clonazepam 0.5–2 mg is effective.

Excess saliva due to an inability to swallow

- Can be treated with anticholinergic drugs but will have significant side effects
- Hyoscine patches behind the ear
- Instillation of atropine drops 0.5% on the tongue two or three times a day
- Botulinum toxin injection or radiation therapy into the parotid glands if unresponsive and problematical

"Freezing":

- especially in doorways: visual, patterned cues across doorway help. Use of "laser cane" to step over beam.

Falls and postural instability

- Occur late in the course of the disease and are unresponsive to medication
- Multidisciplinary assessment with a physiotherapist and occupational therapist to acquire walking aids and make appropriate adaptations

Multiple system atrophy (MSA)

Within the spectrum of MSA:

- Parkinsonism poorly responsive to levodopa
- Striatonigral degeneration
- Olivopontocerebellar atrophy
- Autonomic failure with urinary incontinence and orthostatic hypotension

Overlap occurs with disease progression.

Epidemiology

- Presentation usually in sixth decade
- Life expectancy is around 6 years from onset.
- There are no familial cases reported.

Pathophysiology

- Targeted areas are the striatum, substantia nigra, brainstem nuclei, dentate nuclei of the cerebellum, anteromedial columns of the spinal cord, and Onuf spinal nucleus, which innervates urethral and anal sphincters.
- Pathological specimens reveal argyrophilic neuronal and glial cytoplasmic inclusions positive for alpha synuclein.

Clinical features

- Parkinsonian form (MSA-P) presents with an akinetic rigid syndrome. Tremor is less frequent than in PD.
- Olivopontocerebellar variant (MSA–C) presents with ataxia.

- Autonomic involvement with impotence in men, anorgasmia in women; orthostatic hypotension not due to drugs; urinary urgency and incontinence early in the disease may be a pointer to MSA.
- Bulbar involvement can lead to laryngeal stridor and sleep apnea.
- Pyramidal involvement not severe: brisk reflexes, extensor plantar responses that in a patient with PD could be due to vascular disease or cervical spondylosis
- Other clinical signs:
  - Dusky blue hands due to autonomic involvement
  - Marked antecollis
  - Painful dystonias
  - Low-amplitude myoclonic jerks of the outstretched fingers (polyminimyoclonus)
  - Cognitive problems rare

Investigations

- Autonomic function tests may confirm the clinical findings.
- Sphincter EMG may show denervation of the external anal sphincter (but denervation can also be found in PSP).

MRI

- MSA-P:
  - Atrophy of stratum/putamen > caudate
  - Putaminal hypointensity (posterolateral margin) + thin rim of hyperintense signal
  - Decreased width of pars compacta
- MSA-C (see Fig. 9.2)
  - Pontine atrophy
  - Atrophy of middle cerebellar peduncles, cerebellum + inferior olives
  - T2W hyperintensity ("hot cross bun sign")

Management

- Fifty percent of MSA cases are L-dopa responsive.
- If no response or significant side effects, try amantadine (100 mg bid).
- Orthostatic hypotension:
  - Reduce dopaminergic drugs
  - TED stockings
  - Head up tilt at night
  - High salt intake
  - Fludrocortisone (0.1–0.2 mg at night): side effect, supine hypertension, fluid retention
  - Midodrine (2.5 mg, increase to 10 mg tid): side effect, supine hypertension
- Bladder urgency: oxybutynin 2.5 mg bid, maximum 5 mg tid
- Nocturia: intranasal DDAVP 20–40 μg at night; Side effect, hyponatremia

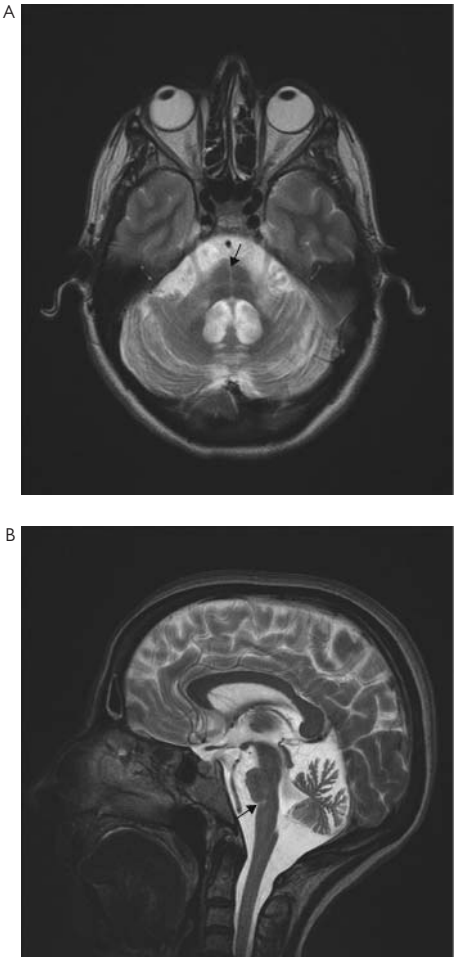

Figure 9.2 Multiple system atrophy: cerebellar type (MSA-C). (A) Axial and (B) sagittal T2-weighted MRI. Profound volume loss in the cerebellar hemispheres, vermis, middle cerebellar peduncles, and brainstem is typical with predilection for the pons and olivary nuclei. (A) Note prominence of intrapontine CSF clefts (black arrow) described as the "hot cross bun" sign. (B) Sagittal MRI demonstrates pontine volume loss with flattening of the anterior surface and widening of the pontomedullary angle (black arrow).

Progressive supranuclear palsy (PSP)

Also called Steele–Richardson–Olszewski syndrome.

Incidence Usual onset in the sixth and seventh decades. The median survival is 7 years from onset.

Pathophysiology

- Tau-positive neurofibrillary tangles found in the pallidum, substantia nigra, periaqueductal grey matter, and superior colliculi
- Frontal cortical involvement

Clinical features

- Presentation with a symmetrical akinetic rigid syndrome with the axial trunk and neck muscles being more affected than the limbs. It can also present with ataxic features.
- Tremor is uncommon.
- Falls backward early in the course of disease.
- Supranuclear gaze palsy affecting downgaze more than upgaze is the most distinctive feature with symptoms of difficulty scanning the printed page and walking downstairs.
- Other features:
  - "Stair case" up gaze
  - Square wave jerks of eyes at rest
  - Inability to converge eyes
  - Surprised look due to frontalis overactivity
  - Growling dysarthria with pallilalia
  - Dysphagia
  - Apraxia of eyelid opening
- Impairment of frontal lobe executive function with a frontal lobe dementia later in the disease with personality change and emotional lability
- Bladder symptoms are unusual and occur late.

Investigations

MRI

- Midbrain atrophy ("Mickey Mouse ears") due to enlargement of 3rd ventricle + interpeduncular fossa + decreased AP diameter of midbrain + depression of superior midbrain on sagittal images ("hummingbird sign").
- T2W hyperintense signal periaqueductal grey matter + globus pallidus
- Frontotemporal atrophy

Management

- Response to levodopa is usually poor.
- Amantadine should be tried.
- PEG tube feeding necessary in severe dysphagia.
- Pneumonia is the most common cause of death.

Corticobasal degeneration (CBD)

Incidence Presents in the sixth and seventh decades.

Pathophysiology

- Degeneration of posterior frontal, inferior parietal, and superior temporal cortices, thalami, substantia nigra, and cerebellar dentate nuclei
- Tau deposition in swollen achromatic neurons

Clinical features

- Striking asymmetry at onset and throughout the disease course usually involving one limb.
- Combination of akinetic rigidity and cortical features. The latter are:
  - Apraxia;
  - Cortical sensory loss (simultagnosia and dysgraphesthesia)
  - "Alien limb phenomenon": hand may interfere with activities of the other arm or grasp onto doors and handles
- Other features:
  - Stimulus-sensitive myoclonus
  - Painful limb dystonia
  - Bulbar problems with dysphagia and dysarthria

Investigations

MRI shows asymmetric cortical atrophy in clinically affected areas.

Management

- Poor response to levodopa
- Clonazepam and sodium valproate may be used for troublesome myoclonus.
- PEG tube feeding may be necessary in severe dysphagia.

Hyperkinetic movement disorders

Hyperkinetic movement disorders are characterized by involuntary movements that are sometimes suppressible for a period of time. The prototypical hyperkinetic movement disorder is HD.

Chorea, athetosis, and ballism

Chorea, athetosis, and ballism represent a continuum of movements of increasing amplitude and explosiveness (see Table 9.5).

- Chorea: rapid, jerky movements of irregular timing
- Athetosis: writhing of limbs, most prominent distally
- Ballism: large amplitude "flinging" of a limb; proximal activation of muscles

Table 9.5 Differential diagnosis of chorea, athetosis, and ballism

Hereditary diseases—neurodegenerative and metabolic	Huntington disease DRPLA, SCA-17 Tourette syndrome Familial benign chorea Wilson disease Halloverden-Spatz (PANK-2) Neuroferritinopathy Neuroacanthocytosis Lesch-Nyhan syndrome Ataxia-telangiectasia
Vascular lesions, anoxia, hypoxia	Subthalamic lesions—hemiballism, hemichorea
Acquired metabolic dysregulation	Hyperosmolar hyperglycemic nonketotic syndrome (hypoperfusion of striatum) Thyrotoxicosis Contraceptive medication
Infectious, inflammatory, and autoimmune	Encephalitis, CJD, SLE, antiphospholipids syndrome, PANDAS, poststreptococcal (Sydenham chorea) Chorea gravidarum
Toxic/drug exposure	Antipsychotics (neuroleptics) Dopamine and dopamine agonists Various anticonvulsants Anticholinergic drugs

Huntington disease

- AD with full penetrance
  - Expansion of CAG trinucleotide repeat >36 repeats
  - Expansion size inversely related to age of onset
  - Increased expansion with each generation—"anticipation"
  - Prenatal diagnosis available

Clinical features

- Onset during fourth and fifth decades
- Movement disorders:
  - Chorea, initially fidgetiness
  - Parkinsonism—juvenile onset Westphal variant
  - Dystonia

- Psychiatric features:
  - Change in personality
- Dementia
- Other features:
  - Slowed saccades
  - Head thrust or blinking to generate saccades
  - Progressive weight loss

Pathophysiology

- Loss of striatal and nigral GABA
- Decreased number of striatal receptors for dopamine and acetylcholine
- Possible defect in mitochondrial energy production
- Gross pathology: atrophy of caudate and lentiform nucleus

Imaging

MRI reflects pathology, demonstrating progressive atrophy of the caudate and lentiform nucleus.

Differential diagnosis

See Table 9.5.

Treatment

- Symptomatic only
- Chorea: dopamine receptor blockers (haloperidol) and presynaptic dopamine depleters (reserpine, tetrabenazine)
- Depression and psychosis: antidepressants and typical or atypical antipsychotic medications
- Close supervision is required as dementia and/or psychosis progress.

Sydenham chorea

Sydenham chorea is one of the major clinical manifestations of acute rheumatic fever (caused by Group A Streptococcus) and the most common form of acquired chorea in children. Incidence has dramatically decreased in developed countries due to availability of antibiotic treatment for Streptococcal infection.

Clinical features

- Chorea: onset 1–8 months after untreated Streptococcal infection
  - Recurrence in 20%–30% of patients 3–10 years after acute event
- Emotional lability may precede chorea.
- Hypotonia, poor fine motor control, weakness

Pathophysiology
- Through the mechanism of molecular mimicry, antibodies produced in response to antigen from Streptococcal infection target neuronal structures in basal ganglia and cortex.

Diagnosis
- Clinical diagnosis based on history and presentation
- Anti-streptolysin O titer may be helpful
  - Present in 80%
  - Positive at low titer with other infections

Differential diagnosis
See Table 9.5.

Treatment
- Prednisone (1 mg/kg daily x 2 weeks, then taper over 2–3 weeks)
  - Valproate or carbamazepine as alternative to steroids
  - Neuroleptic medications for refractory or severe cases
- Penicillin daily x 10 days or as depot injection
  - Erythromycin an alternative if allergies to penicillin

Tremor

Tremor is the involuntary rhythmic oscillation of a body part caused by synchronous or alternating contraction of antagonist muscle groups. Tremor may be classified on basis of frequency of oscillation and by the setting in which it occurs (e.g., at rest, with intentional movement). A high-frequency physiologic tremor (10–12 Hz) is present in all persons but not usually appreciated unless enhanced by anxiety, fatigue, or metabolic dysregulation (e.g., thyrotoxicosis).

Diagnosis (see Table 9.6)
- Assess setting
  - Rest tremor—occurring at rest
  - Postural-action tremor—present with certain postures or actions without variation
  - Intention tremor—action tremor that increases in amplitude as goal neared or with specific activity
- Assess frequency
- Consider symmetry, limbs involved, associated symptoms

Table 9.6 Differential diagnosis of tremor

Tremor	Setting	Frequency	Associations
Physiologic	Postural-action	10–12 Hz	Precipitating factors: fatigue, anxiety, medications, metabolic dysfunction
Essential	Postural-action	4–6 Hz	Prominent in hands/arms; may involve head and voice
Parkinson disease	Rest and Postural-action	4–6 Hz	Asymmetric; "pill-rolling" tremor In hand; can involve legs and feet; rarely involves head; other Parkinsonian features on exam
Cerebellar	Postural-action or intention	3–4 Hz	Cerebellar signs: ataxia and dysmetria
Orthostatic	Postural tremor	14–18 Hz	Prominent in legs/feet when standing; suppressed by walking or leaning on support; can affect arms also
Rubral	Rest, postural or intention	2–5Hz	Signs of brainstem or cerebellar damage
Neuropathic	Variable	Variable	Signs of peripheral neuropathy

Essential tremor

Most common cause of postural-action tremor worldwide

- Prevalent in ~5% of population
- Familial (AD) or sporadic
- Incidence increases with age, though familial tremor may present at earlier ages

Diagnosis

- Bilateral postural-action tremor of forearms/hands
- Head/voice may be involved; rarely will legs/feet be involved.
- No sign of dystonia
- Present for >3 years
- Positive family history
- Response to alcohol

Treatment

- Propranolol 60–320 mg/day or may use single dose for anticipated social or performance situations
  - Primidone 12.5–750 mg/day as alternative to propranolol
  - Propranolol + primidone used together may be more effective than either used alone.
- For nonresponders to propranolol and/or primidone:
  - Atenolol
  - Gabapentin

- Topiramate
- Botox A

- Surgical intervention in failed medical therapy and with severe disability
  - Unilateral thalamotomy
  - Thalamic deep brain stimulation (DBS)

Though ET will respond to alcohol and to benzodiazepines such as alprazolam, it is best to avoid these due to potential for addiction.

Dystonias

Dystonias represent the most common movement disorder after PD. Dystonia is characterized by sustained agonist/antagonist muscle contractions, which may involve any muscles—limb, axial, or cranial. Dystonias may be hereditary (multiple genes have been identified and more are being elucidated) or acquired; may occur at rest or with action; may be sustained, intermittently triggered, or rhythmic.

- Action dystonia—worsened during voluntary movements of affected body part or segment
- Overflow dystonia—worsened during voluntary action of any body part or segment, unrelated to the affected body part or segment. Talking is most common trigger of overflow dystonia.
- Task-specific dystonia—worsened with specific voluntary action
- Torsion dystonia—muscle contractions cause a twisting movement
- Dystonic tremor—rapid spasms of muscles in repetitive pattern
- Dystonic storm = status dystonicus: sudden increase of established dystonia, which may result in rhabdomyolysis and renal failure; a rare phenomenon usually seen only in children or adolescents

Dystonic movements can be more severe with fatigue, stress, and strong emotion. They are relieved by rest and during sleep unless quite severe. Dystonias may be classified by age of onset (0–12 years, 13–20 years, >21 years), by anatomic distribution (focal, segmental, multifocal, generalized, or hemi-body), or by etiology (primary/idiopathic, dystonia plus, secondary, associated with heredodegenerative diseases)

Etiology

Primary dystonias

A diverse group of familial and sporadic dystonias of which dystonic postures or movement are the only neurological abnormalities. At least four gene loci have been identified (DYT1, DYT6, DYT7, and DYT13). The best-characterized and most representative of the primary dystonias is Oppenheim dystonia.

Primary (Oppenheim) dystonia

- Prevalence 1:3000. Common in Ashkenazi Jews but seen in other ethnic groups also
- AD:
  - DYT I gene on chromosome 9 (coding for torsin A protein)
  - Low penetrance (30%)
  - Variable expression

Clinical features

- Childhood onset
- Initially focal (foot); variable spread to segmental or generalized. In advanced cases, body parts may remain in fixed postures.
- Craniocervical muscles are usually spared.

Adult-onset primary dystonias

- Prevalence in United States ~30/100,000
- Increased rates of dystonia among family members suggests underlying genetic contribution.
- Usually localized to specific muscles or body segments
  - Cervical dystonia—most common of localized dystonias
  - Facial dystonia—blepharospasm or oromandibular dystonia
  - Hand/arm—writer's or musician's cramp
  - Vocal cords—spastic dysphonia (vocalis muscle contraction) or breathy dysphonia (posterior cricoarytenoid contractions)
- Botulinum toxin may provide relief of localized dystonias.

Dystonia plus syndromes

- Dystonia coexists with Parkinsonism or myoclonus. The most important (treatable) of all the dystonic syndromes is dopa-responsive dystonia.

Dopa-responsive dystonia (DRD)—Segawa disease

- AD:
  - Mutation in gene for GTP cyclohydrolase 1
  - AR form due to mutation in tyrosine hydroxylase gene.

Clinical features

- Childhood lower limb onset progressing to generalized dystonia
- Diurnal variation in symptoms
- Mild parkinsonism
- Paraparesis presentation
- Also cases described similar to cerebral palsy
- Exquisite response to L-dopa

Management

- Therapeutic trial of L-dopa in all cases of dystonia <30 years: Sinemet 275 tid for 3 months

In equivocal cases, perform phenylalanine loading test, checking phenylalanine and tyrosine blood levels at several time points. An elevated phenylalanine/tyrosine ratio at 4 hours is highly sensitive and specific for DRD.

Secondary dystonias

Result of insult or injury to the central or peripheral nervous system or as a drug-induced phenomenon. Causes are myriad and include trauma, vascular insults, infection, tumors, rheumatological disorders, toxic/metabolic insults, and psychogenic disorders. A careful clinical history is essential to identify or exclude a secondary dystonia and should direct the following workup:

- Laboratory studies (complete blood count, comprehensive metabolic studies, PTH, HIV, ANA, antiphospholipids, suspected toxins)

- Lumbar puncture (CJD, MS, infectious)
- Imaging of the neuraxis
- NCS/EMG if peripheral nerve injury suspected

Dystonia and heredodegenerative diseases

Dystonia may be part of a number of inherited degenerative or metabolic diseases. Dystonia is late developing or part of a complex of symptoms. The associated nondystonic symptoms lead to diagnosis and are clues that the syndrome is not primarily a dystonic syndrome.

Treatment of dystonia

- Always consider trial of L-dopa therapy
- Botulinum toxin trial if possible
- Pharmacological therapy:
  - Anticholinergic (trihexyphenidyl)
  - Baclofen (up to 80–120 mg/day in divided doses)
  - Benzodiazepines (clonazepam, diazepam)
  - Antidopaminergics
- Surgical interventions
  - Intrathecal baclofen
  - DBS of the internal globus pallidus has replaced cervical rhizotomy, thalamotomy and pallidotomy as surgical treatment of choice when symptoms otherwise uncontrolled and disabling.

Myoclonus

Myoclonus is characterized by rapid (<100 msec in duration) discrete simple jerks of a body part through involuntary activation (or inactivation) of muscle.

- Positive myoclonus: brief activation of muscle (myoclonus)
- Negative myoclonus: inactivation of muscle (asterixis)

Clinical manifestations

- Single or repetitive muscle jerks elicited by excessive discharge from a group of neurons
- Irregular and unpredictable usually but can occur rarely in bursts or rhythmically
- Can be stimulus sensitive
- Essential or physiological myoclonus not uncommon at interface of sleep and wake (hypnic jerks) or during sleep (periodic limb movements of sleep)

Classification

- Clinical
  - At rest, with action, or with intention
  - Focal, segmental, multifocal, or generalized
  - Irregular, oscillatory, rhythmic

- Generator
  - Cortical—with EEG correlates
  - Thalamic
  - Brainstem
  - Spinal
  - Peripheral (through ephaptic transmission of nerve impulses—usually secondary to demyelination—rare)
- Etiology
  - Essential (physiological, periodic limb movements of sleep, occurring at interface of sleep/wake, hiccoughs)
  - Epileptic (epilepsia partialis continuans, myoclonic epilepsies)
  - Symptomatic (see Table 9.7)

Investigations

- Guided by type of myoclonus and associated features
- MRI may be indicated if central lesions suspected
- EEG to assess for spike correlates of cortical myoclonus—though may be false negative (normal)
- Review of drug and toxin exposure
- General metabolic workup (liver/kidney function, electrolytes, complete blood count)
- Infectious or paraneoplastic workup if indicated
- Review of family history

Treatment

- Valproate
- Clonazepam
- Levitiracetam
- Piracetam
- Primidone

Myoclonic syndromes of note

Palatal myoclonus: primary or secondary

- 2 Hz rhythmic tremor
- Secondary form due to lesion in Guillain-Mollaret triangle of brainstem (defined by dentate nucleus of cerebellum, olivary, and red nuclei of brainstem)
- The only movement disorder that persists during sleep (if secondary in etiology)
- May be associated with ocular myoclonus
- Patients may note clicking sound in ears

Lance-Adams syndrome

- Acquired syndrome after hypoxia, most commonly seen after cardiopulmonary resuscitation
- Myoclonic jerks with action; also cerebellar ataxia
- Myoclonus can develop days or weeks after acute hypoxic event
- Myoclonus worst with actions requiring greatest fine motor control

Table 9.7 Symptomatic cause of myoclonus

Cause	Examples
Widespread encephalopathy and metabolic dysregulation	Asterixis (negative myoclonus) or (positive) myoclonus
Vascular lesions	Focal myoclonus
Dementias	
Infectious and inflammatory	Whipple disease, subacute sclerosing panencephalitis (SSPE)
	Inflammatory myelitis
Toxic	Anti-convulsants, dopamine agonists, stimulants, opioids, some antibiotics, etc.
Paraneoplastic	Autoimmune
Neurodegenerative	Lafora body disease, prion disease (CJD)
Hypoxic	Lance Adams syndrome
Traumatic	Focal myoclonus
Metabolic storage diseases	Wilson disease
Spinocerebellar degeneration syndromes	Often associated with ataxia

Opsoclonus-myoclonus syndrome
- "Dancing eyes, dancing feet": rare autoimmune disorder
- Polyminimyoclonus—muscle jerks are of small amplitude
- Involuntary chaotic saccades of eyes
- Pathognomonic for neuroblastoma in children, but it can also be seen in postviral and paraneoplastic syndromes in children and adults

Myoclonic startle syndromes

Hyperekplexia

Startle stimulus may provoke an exaggerated and complex involuntary motor response, leading to a fall.

Tics

Involuntary simple or complex movement or vocalization that may be suppressed for brief periods of time but "bursts through" as inner urge or unpleasant sensation increases—and then is relieved as tic occurs.
- Common in childhood with transient tic disorders (symptoms persisting less than 1 year) seen in up to 25% of children
- Most common presentation is with eye blinking, facial grimace, or head shaking; more severe cases may involve limbs.

- Simple tics require no treatment and often resolve spontaneously.
- Simple tics difficult to distinguish from other movement disorders. Distinguishing characteristics of a tic are as follows:
  - Building premonitory sensation
  - Intermittency
  - Suppressibility
- Consider secondary causes of tic when onset (in children or adults) is sudden or tics are severe:
  - Neuroacanthocytosis
  - Medication use (e.g., neuroleptics, dopamine agonists)
  - Infection (e.g., PANDAS or encephalitis)
  - CJD
  - Head trauma, stroke

Tourette syndrome

Tourette syndrome is the most common of the persistent (>1 year duration) tic disorders and is characterized by multiple motor and vocal tics, with onset at about 5 years of age (though has been noted as early as 2 years of age), worsening of tics with peak at about 10–11 years of age, and decline in severity with 50% of patients having resolution of symptoms by age 18. Recurrence in adulthood can occur. Common comorbidities include ADHD, OCD, and behavioral issues (e.g., impulse control). More common in boys than girls (4.3:1 in one large registry).

Diagnostic criteria

- Multiple motor tics and one or more vocal tics must be present at some time, though not necessarily concurrently
- Tics must occur multiple times daily or intermittently for >1 year.
- Anatomical location, frequency, type, complexity, or severity of tics must change over time
- Onset of tics before age 21
- Motor and vocal tics must be substantiated by reliable observer.
- No other alternative explanation for tics can be found.

Pathophysiology

- Thought to be inherited dysregulation in the striatal-thalamic-cortical spinal system resulting in disinhibition in the motor and limbic systems
- PET studies demonstrate increased dopamine storage and release in the striatum.

Treatment

- None required if patient not troubled physically or socially by symptoms. Reassurance given; tics may remit.
- Pharmacological management
  - Dopamine antagonists (e.g., fluphenazine, pimozide, and tetrabenazine)
  - Dopamine agonist (e.g., ropinirole)
  - Alpha adrenergic agonists (e.g., clonidine, guanfacine)
  - SSRIs

- Botulinum toxin—for focal motor or vocal tics
- Treatment of ADHD (common in patients with Tourette syndrome) with stimulants may worsen tics.
- Consider comorbidities in choosing treatment options:
  - Tourette + ADHD: methylphenidate or dextroamphetamine
  - Tourette + OCD: SSRIs
  - Tourette + impulsive behavior: clonidine or guanfacine

Ataxia

Ataxia ("without control") refers to loss of coordination of voluntary movements; cerebellar ataxia represents damage or dysfunction of the cerebellum and/or its afferent or efferent pathways. Incoordination may affect voluntary muscular function of limbs, trunk, vocal cords, and eye muscles resulting in:

- Postural and/or gait instability
- Dysmetria: undershoot or overshoot of intended movement to a target
- Dysdiadokinesia: inability to perform rhythmic movements

Ataxia also results if the sensory organs feeding information to the cerebellar afferent pathways are damaged:

- Vestibular ataxia: damage to the vestibular system. Key features are nausea, vomiting, vertigo, and disequilibrium.
- Sensory ataxia: severe loss of peripheral sensory nerves responsible for proprioception. The cerebellum is hindered in its function as it receives no feedback on where a body part is in space at any given time. Severe sensory ataxia may result in inability to stand, to maintain a sitting posture, or to manipulate objects in the environment.

Cerebellar ataxias may be classified into hereditary, sporadic, and acquired forms. Hereditary forms may be classified by young onset (<21 years) versus older onset (>21 years) or by type of inheritance (autosomal dominant, autosomal recessive, X-linked, and sporadic). In general, autosomal dominant cerebellar ataxias are of late onset; autosomal recessive cerebellar ataxias are of young onset; however, exceptions occur.

Mitochondrial disorders (e.g., Leigh syndrome, MELAS, MERFF) and many hereditary metabolic disorders (e.g., storage disorders, urea cycle disorders, aminoacidurias, disorders of lactate/pyruvate metabolism, sialidosis, myoclonic epilepsies) may have associated intermittent or progressive ataxia; however, this is often not the most prominent or defining feature of the disorder.

Hereditary ataxias

The hereditary ataxias are often recognized and classified by their manner of inheritance and their associated symptoms and signs, which help direct genetic testing to elucidate underlying defect.

Autosomal dominant cerebellar ataxias (SCA 1–8, 9–22, 25, DRPLA, and the episodic ataxias EA 1–7)

Common characteristics

- Onset of ataxia in young adult or mid-adult years (though wide variation)
- Gait ataxia and falls, prominent early in course
- Limb ataxia and dysarthria
- Hyperreflexia early in course with later hypo- or areflexia
- Loss of vibratory perception and proprioception late in course
- Nystagmus, slow saccades, abnormal pursuit with eye movements
- Anticipation (earlier onset and more severe disease seen in succeeding generations) related to unstable trinucleotide repeat abnormality (CAG–glutamine) in many of the dominant ataxias.

Each of the autosomal dominant SCAs has distinguishing clinical features and an underlying genetic abnormality that aid in identification (Table 9.8). They also may be thought of in more general terms and grouped accordingly (see Table 9.9).

Episodic ataxias

- Intermittent self-resolving episodes of cerebellar ataxia
- Seven identified; EA-1 and EA-2 most common (both are channelopathies). See Table 9.10
- Different mutations in the CACNA1A gene associated with EA2 are responsible for SCA6 and hemiplegic migraine.

Table 9.8 Clinical features of autosomal dominant cerebellar ataxias

ADCA	Gene/protein	Clinical characteristics
SCA1	Chr 6; CAG repeats; ataxin-1	Pyramidal signs, peripheral neuropathy, dysphagia, ophthalmoparesis
SCA2	Chr 12; CAG repeats; ataxin-2	Slow saccades, peripheral neuropathy, dementia
SCA3	Chr 14; CAG repeats; ataxin-3	Pyramidal and extrapyramidal signs, peripheral neuropathy, amyotrophy, ophthalmoparesis
SCA4	Chr 16	Sensory neuropathy
SCA5	Chr 11; beta-2 spectrin	Pure ataxia, slowly progressive
SCA6	Chr 19; CAG repeats; alpha 1A P/Q calcium channel subunit	Mild ataxia of late onset; downbeat nystagmus

Table 9.8 (*Contd.*)

ADCA	Gene/protein	Clinical characteristics
SCA7	Chr 3; CAG repeats; ataxin-7	Macular degeneration
SCA8	Chr 13; CTG repeats	Hyperreflexia, decreased vibratory sense, maternal bias for transmission
SCA10	Chr 22; ATTCT repeats; ataxin-10	Generalized or complex partial seizures; peripheral neuropathy
SCA11	Chr 15	Mild ataxia, slowly progressive; hyperreflexia; vertical nystagmus
SCA12	Chr 5; CAG repeats; protein phosphatase	Tremor, dementia, dystonia, bradykinesia, dysautonomia, hyperreflexia
SCA13	Chr 19; potassium channel KCNC3	Mental retardation, short stature
SCA14	Chr 19; protein kinase C	Axial myoclonus
SCA15	Chr 3	Pure ataxia/dysarthria
SCA16	Chr 8	Head tremor, nystagmus
SCA17	Chr 5; CAG repeats; TATA binding protein	Dementia, parkinsonism, dystonia, chorea, seizures
SCA18	Chr 7	Pyramidal signs, weakness, peripheral neuropathy
SCA19	Chr 1; allelic with SCA 22	Tremor, myoclonus, cognitive impairment
SCA20	Chr 11	Palatal tremor/myoclonus, pyramidal signs, dentate calcification on CT
SCA21	Chr 7	Tremor, cognitive impairment, extrapyramidal signs of akinesia, and rigidity
SCA23	Chr 20	Distal sensory deficits
SCA25	Chr 2	Sensory neuropathy, facial tics, GI symptoms
SCA26	Chr 19	Pure cerebellar ataxia
SCA 27	Chr 13; fibroblast growth factor	Cognitive impairment
SCA28	Chr 18	Ophthalmoparesis, ptosis
DRPLA	Chr 12; atrophin-2 related protein	Early-onset myoclonus and epilepsy, late-onset chorea; dementia
16q22.1	Chr 16; puratrophin-1	Decreased muscle tone

Table 9.9 Characteristics of autosomal dominant cerebellar ataxias (ADCA): Harding classification

Clinical features	Gene
ADCA type I (complex) ± Pyramidal signs ± supranuclear ophthalmoplegia ± extrapyramidal signs ± peripheral neuropathy ± dementia	SCA 1–4, 10, 12–14, 17–21, 23–25, 27–28, DRPLA, 16q22.1-linked
ADCA type II Pigmentary retinopathy ± any other signs for type I (above)	SCA7
ADCA type III Pure cerebellar ± mild pyramidal signs. Late onset	SCA 5, 6, 8, 11, 15, 16, 26

Table 9.10 Characteristics of episodic ataxias EA1 and EA2

Features	EA1 (with interictal myokymia)	EA2 (with interictal nystagmus)
Age at onset (years)	3–20	3–30
Duration of attack	Minutes	Hours–days
Triggers for attack	Spontaneous, startle, exercise	Stress, exercise, fatigue, fever, alcohol, phenytoin
Associated symptoms (in addition to ataxia) during attacks	Dysarthria, shaking tremor, twitching	Dysarthria, nausea, vertigo, diaphoresis, headache, tinnitus, ptosis, ocular palsy
Response to acetazolamide	+/–	++
Progressive ataxia	No	Sometimes
Gene	K^+ channel, KCNA1	Na^+ channel, CACNA1A

Autosomal recessive cerebellar ataxias

- Age of onset generally under 21 years (with notable exceptions)
- Heterogeneous group of ataxias
  - Friedrich ataxia and variants (most common AR ataxia). (See Box 9.1.)
  - Ataxia telangiectasia
  - Ataxias (1 and 2) with oculomotor apraxia
  - Ataxia of Charlevoix-Saguenay
  - Ataxia with vitamin E deficiency
  - Infantile-onset SCA
  - Marinesco–Sjogren syndrome
  - Ramsay–Hunt syndrome

Box 9.1 Highlight on Friedrich Ataxia

Trinucleotide (GAA) mutation in frataxin gene. Ninety-six percent have an expansion in both alleles. Others have a point mutation in one allele and expansion in other. Diagnosis excluded if two normal sized alleles.

Clinical features

- Gait ataxia, usual onset in children or teens, but can begin in later adult life
- Pyramidal weakness and signs, extensor plantars
- Axonal peripheral neuropathy (absent ankle jerks)
- Optic atrophy leading to mildly decreased visual acuity
- Abnormal eye movements: nystagmus (25%), broken pursuit, hypometric saccades, macrosaccadic square wave jerks
- Deafness (10%)
- Skeletal abnormalities: pes cavus (50%) and scoliosis (75%)
- ECG abnormalities: widespread T wave inversion. Screen for hypertrophic cardiomyopathy (25%)
- Diabetes or glucose intolerance (20%)
- Mean age of death: mid-30s through infection or cardiac arrhythmias or heart failure

Late-onset forms occur with retained reflexes and lower limb spasticity and are without ataxia and/or cardiomyopathy.

Pathophysiology

Lack of or abnormal frataxin (a mitochondrial protein whose function is not fully elucidated but felt to be an antioxidant through its involvement in iron metabolism)

Studies

- MRI: dorsal column and cerebellar atrophy
- NCS/EMG: demyelinating peripheral neuropathy
- ECG abnormalities
- Genetic testing is confirmatory.
- Always check vitamin E levels because vitamin E deficiency is a treatable mimic.

X-linked cerebellar ataxias

- Rare except for Fragile X–tremor ataxia syndrome (CCG trinucleotide expansion)
- Heterogeneous
  - Fragile X–tremor ataxia syndrome (presentation in adult males). (See Box 9.2.)
  - Pure ataxia of early onset (childhood or adolescent onset)
  - Ataxia and spastic paraplegia (childhood or adolescent onset)
  - Ataxia, deafness, optic atrophy, hypotonia (infantile onset)
  - X-linked sideroblastic anemia with (nonprogressive) cerebellar ataxia

Box 9.2 Highlight on Fragile X-tremor ataxia syndrome (FRXTAS)

Trinucleotide (CCG) expansion in the FMR1 gene responsible for Fragile X syndrome (common cause of mental retardation in males)

- <55 repeats: normal
- 55–200 repeats: FRXTAS
- >200 repeats: Fragile X syndrome

Clinical features

- Presentation in older males with carrier prevalence as high as 1:800
- Presentation in women through inactivation of normal X
- Ataxia and postural tremor
- Other features can include cognitive deficits, parkinsonism, proximal lower limb weakness, and peripheral neuropathy.
- MRI imaging with generalized brain atrophy and high T2 signal in middle cerebellar peduncles

Genetic testing recommended for:

- Men >50 years old with unexplained ataxia
- Men >50 years old with action tremor, cognitive decline or parkinsonism in setting of family history or persons with premature ovarian failure, mental retardation, autism, or developmental delay
- Men >50 years old with middle cerebellar peduncle sign on MRI

Sporadic ataxias

- Often present late in adulthood: after age 40, commonly in seventh decade
- Sporadic mutation of known ADCA sometimes identified
- Can have rapidly progression of ataxia
- Less likely (than in autosomal dominant cerebellar ataxias) to have associated noncerebellar degenerative symptoms
- Parkinsonism and upper motor neuron signs common
- Associated autonomic dysfunction may lead to classification as MSA

Acquired ataxias

Any insult within the cerebellum or its pathways may result in ataxia. Acquired causes are diverse and include the following:

- Vascular issues: stroke or vascular malformation
- Neoplasm or paraneoplastic disorder (see Table 9.11)
- Autoimmune or inflammatory disease (MS, sarcoid, SLE)
- Toxic/metabolic: Vitamin (E, B_{12}) deficiency, copper deficiency, hypothyroidism, alcohol abuse

A careful history and examination guides diagnostic procedures.

Table 9.11 Paraneoplastic disorders resulting in ataxia, associated antibodies, and cancer types

Syndrome	Paraneoplastic antibody	Associated cancer
Subacute cerebellar degeneration	anti-Hu	SCLC
	anti-PCA-2	
	anti-Yo	Ovary, breast
	anti-Ta/Ma2	Testis
	Anti-Ri	Breast
	Anti-Tr	Hodgkin's lymphoma
Subacute sensory neuropathy/ neuronopathy resulting in sensory ataxia	Anti-Hu	SCLC
	Anti-amphiphysin	SCLC
	ANNA-3	SCLC
	Anti CRMP5/CV2	SCLS, thymoma

Anti-PCA-2, anti-Purkinje cell antibody; SCLC, small-cell lung cancer.

Chapter 10

Sleep disorders

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Approach to the patient with a sleep disorder

- As sleep disorders and sleep-related complaints occur commonly, the clinician should use a systematic approach to consider currently described diagnostic categories and develop appropriate treatment options.
- Patients with sleep complaints usually present with one or more of three types of problems:
  - Insomnia
  - Abnormal movements, behaviors, or sensations during sleep or nocturnal awakenings
  - Excessive daytime sleepiness
- As in any other diagnostic evaluations, begin with a full history of the sleep-related complaint.
- Ideally, the evaluation includes a history from the patient's bed partner for comments on intensity of snoring and presence of apneas and abnormal behaviors.
- Questions about the sleep–wake schedule are important.
  - Sleep schedule: time to bed, time to sleep onset, number and times of awakenings, time of final awakening
  - Waking schedule: naps, meals, alcohol, times and doses of medications, times and amounts of alcohol, caffeine, nicotine

Sleep physiology

- Sleep is an active process that includes alterations in the physiology of most organs and systems.
- Sleep stages are classified based on three measures: electroencephalogram (EEG), eye movements obtained by electrooculography (EOG), and muscle tone as assessed by electromyography (EMG) of the mentalis muscle.
- There are two major states: non-rapid eye-movement sleep (NREM) and rapid eye movement sleep (REM)
  - These alternate cyclically across sleep episodes.
  - State characteristics:
    NREM sleep: synchronous EEG; low muscle tone; four stages
    REM sleep: desynchronized EEG, muscles are atonic, dreaming is typical; one stage

NREM sleep

- Stage 1—also known as drowsiness; low-voltage, mixed-frequency EEG, slowly rolling eye movements
- Stage 2—moderate low-voltage EEG; hallmark is sleep spindles (bursts of 12–15 Hz activity, lasting 0.5–2 seconds); K complexes (brief high-voltage discharges with an initial negative deflection followed by a positive component)

- Stage 3—high amplitude delta (2 to 3 Hz) activity occupying 20%–50% of the background
- Stage 4— similar to stage 3 except that delta activity comprises more than 50% of the EEG record
  - Expressed when a network of neurons in the anterior and posterior hypothalamus, midbrain, and brainstem create conditions that favor decreased metabolic rate and promote neuronal synchrony through the thalamus

REM sleep

- EEG is of lowest voltage mixed frequency activity; intermittent bursts of rapid conjugate eye movements (REM) occur; tonic chin EMG activity is absent or markedly reduced (reflection of muscle paralysis resulting from active inhibition of muscle activity), phasic muscle discharges occur in irregular bursts
- Activation of cholinergic neurons occurs in the pontine dorsal tegmentum, causing activation of reticular neurons in the medulla with subsequent loss of muscular movements, but with rapid eye movements.
- REM sleep is inhibited by activation of the dorsal raphe and locus ceruleus.

Diagnostic procedures

Clinical polysomnography (PSG)

- Simultaneous recording of sleep and multiple variables
- Variables include: EEG, EOG, mentalis EMG, surface EMG of the anterior tibialis muscle (for detection of leg movements in sleep), electrocardiogram (ECG), measurement of nasal and oral airflow, respiratory effort, oxygen saturation

Multiple sleep latency test (MSLT)

- A series of four to five nap opportunities with sleep recordings at 2-hour intervals throughout the day
- Typically done after one night of PSG recording to evaluate for underlying sleep disorders such as narcolepsy
- Nap is terminated 15 minutes after sleep onset.
- If no sleep occurs, session is terminated after 20 minutes.

Classification of sleep disorders

International Classification of Sleep Disorders, version 2 (ICSD-2), published in 2005, combines a symptomatic presentation (e.g., insomnia) with one organized in part on pathophysiology (e.g., circadian rhythms) and in part on body systems (e.g., breathing disorders).

ICSD-2 has eight major categories:
- Insomnias
- Sleep-related breathing disorders
- Hypersomnias not due to a breathing disorder
- Parasomnias
- Circadian rhythm sleep disorders
- Sleep-related movement disorders
- Isolated symptoms, apparently normal variants, and unresolved issues (not included here)
- Other sleep disorders (not included here)

Insomnias

Definition Difficulty falling asleep, maintaining sleep (frequent awakenings with inability or difficulty returning to sleep), or early awakening, combined with impaired daytime functioning (fatigue, irritability, inattention).

Classification

Primary insomnias
- Psychophysiological: acute (adjustment sleep disorder)
- Chronic
  - Idiopathic
  - Sleep state misperception

Secondary insomnias
- Sleep disorders (sleep apnea, periodic leg movement disorder, restless leg syndrome)
- Psychiatric disorders (depression, anxiety, panic attacks)
- Inadequate sleep hygiene
- Environmental sleep disorders
- Drugs (nicotine, ethanol, caffeine)
- Medical conditions/medications
  - Fibromyalgia and chronic pain syndromes
  - COPD and other respiratory disorders
  - Medications (beta-blockers, theophylline)
- Circadian disorders
  - Delayed sleep-phase syndrome
  - Advanced sleep-phase syndrome
  - Shift work or jet lag syndrome

Epidemiology
- Overall, 10%–20% of adults report chronic insomnia.
- More prevalent in women than men (3:2)
- Higher rates in elderly (over 65 years of age), unemployed people, low educational levels

Clinical features
- Common complaints
  - Difficulty falling asleep (sleep-onset insomnia)
  - Frequent nighttime awakenings with inability to return to sleep

  - Early morning awakenings
- Daytime symptoms
  - Sense of nonrestorative sleep
  - Irritability
  - Mood changes
  - Anxiety
  - Poor concentration and attention
  - Decline in work performance

Diagnosis

- Careful history and clinical interview
- Review of patient sleep diary (ideally completed for 2 weeks prior to initial evaluation)
- Polysomnography (PSG)—minor role, generally not indicated in evaluation of insomnia (except to rule out periodic leg movements of sleep, sleep apnea, or if insomnia is severe and does not respond to conventional therapy)

Differential diagnosis

- Psychiatric illnesses (depression, anxiety disorders)
- Primary sleep disorders: periodic limb movement disorder (PLMD), restless leg syndrome (RLS), sleep-related breathing disorders
- Circadian rhythm disorders
- Parasomnias

Treatment

- Should target the underlying cause; therefore, often a single approach may not be sufficient
- Education about better sleep hygiene
- Treatment of any underlying psychiatric disorder
- Proper timing of medications used to treat a medical disorder
- Behavioral therapy—relaxation therapy, stimulus control, sleep hygiene, potentially sleep restriction
- Hypnotic medications—most helpful in acute insomnia; should be limited to a 2–4 week course if possible, to avoid dependence
- Commonly prescribed hypnotics
  - Benzodiazepines: Flurazepam (Dalmane), Clonazepam (Klonopin), Temazepam (Restoril), Triazolam (Halcion)
  - Nonbenzodiazepines: Zolpidem (Ambien), Zaleplon (Sonata)

Sleep-related breathing disorders

Breathing during sleep

- Respiratory patterns change according to sleep stage
  - NREM sleep

    Occasional pauses in breathing near sleep onset

    Some breathing periodicity during lighter stages of sleep

    Regular breathing during stage 3–4 (delta wave or slow wave sleep)
  - REM sleep

Inspiratory time decreases and breathing becomes more irregular.

- Regulation of breathing is unique, under both voluntary and automatic control.
- Control of breathing pattern becomes entirely involuntary with sleep onset, with increased regularity in respiration during NREM sleep.
- Response to high CO_2 levels and low oxygen levels is blunted during both slow-wave sleep (stage 3,4) and REM sleep.

Snoring

- Produced by the vibration of soft tissues of the upper airways
- Can occur during inspiration or expiration
- Loudest and most frequent during slow wave sleep, softest during REM sleep
- A cardinal symptom of obstructive sleep apnea (OSA), but its absence does not exclude the diagnosis
- Simple snoring: patients with snoring and no symptoms and signs of OSA
- May increase the risk of cardiovascular diseases and eventual development of obstructive sleep apnea (OSA)

Sleep apnea

- Apnea: absence of ventilation, with absence of airflow, for at least 10 seconds
- Hypopnea: partial reduction of airflow from the preceding baseline, for 10 seconds or longer
- Both respiratory events are associated with oxygen desaturations and arousals and tend to be more frequent during lighter stages of NREM and REM sleep.

Obstructive sleep apnea (OSA)

OSA-hypopnea syndrome (OSAHS) is one of the most common sleep disorders and the most common form of sleep apnea.

Epidemiology

- General population or community-based cohort studies of patients between 30 and 60 years of age estimate that 2%–5% of the population have OSAHS.
- Higher incidence in men (2.5 times more common) than in women
- Prevalence tends to be higher in African Americans, independent of the effects related to obesity

Clinical presentation

- Snoring
- Excessive daytime sleepiness or fatigue
- Witnessed apneas
- Dry mouth, sore throat
- Excessive nighttime sweating

- Insomnia
- Impaired daytime efficiency
- Diminished intellectual performance
- Morning or nocturnal headache, irritability, or personality change
- Depression
- Decreased libido or impotence
- Predisposing factors: obesity, narrow nasal passage, long soft palate, enlarged tonsils, retroflexed mandible

Systemic effects

- Systemic hypertension
- Pulmonary hypertension
- Diabetes mellitus
- Cardiac enlargement, myocardial infarction
- Hypoxemia
- Stroke
- Poor memory or impaired attention
- Increased risk of sudden death during sleep

Complications

- Life-threatening vehicular and occupational accidents
- Failure to gain weight and growth in infants and children

Diagnostic evaluation

- Clinical history of snoring and observed apneas/hypopneas, excessive daytime sleepiness
- Standard polysomnography
- Monitoring of intraesophageal pressure (measures respiratory effort) or end-tidal CO_2

Treatment

- Goal is to keep the airway open during sleep
- Determine severity of illness to select the appropriate treatment
- Apnea-hypopnea index (AHI)—an overall index of the frequency of respiratory disturbance
  - Mild: 5–14 events/hr
  - Moderate: 15–30 events/hr
  - Severe: >30 events/hr
- Continuous positive airway pressure (CPAP):
  - Most common and effective treatment
  - Constant air pressure is generated by a small pump and delivered via tubing to a nasal mask.
- Upper airway surgery on posterior soft palate and uvula
- Oral appliances—used during sleep to advance the lower jaw
- Weight loss
- Supplemental oxygen

Central sleep apnea (CSA)

Characteristics

- Pauses in breathing without ventilatory effort or cessation in airflow of at least 10 seconds associated with absence of respiratory effort
- Occasional central apneas may be seen in patients with OSA.
- Central apnea syndrome: the majority of apneic events are central in origin (50%–80%)

Clinical features

- Insomnia with difficulty falling asleep and frequent awakenings
- Restless unrefreshing sleep
- Two major groups
  - With hypoventilation during the day (hypercapnic): includes patients with a defect in ventilatory control and with neuromuscular disorders
  - Without hypoventilation during the day (nonhypercapnic): patients with Cheyne-Stokes breathing and patients in whom no obvious cause for the CSA exists
- Cheyne-Stokes breathing—crescendo-decrescendo periodic pattern of breathing seen in patients with congestive heart failure, most prominent during lighter stages of NREM sleep, associated with central apneas or central hypopneas at the nadir; arousals tend to occur at the maximum point of respiratory effort
- Cardiac and neurological work-ups are recommended in patients with CSA.

Treatment

- Nasal CPAP may be useful in CSA associated with upper airway obstruction and congestive heart failure.
- BiPAP often shows greater benefit, as it produces higher pressure during inspiration than expiration; thus, the pressure difference may stimulate inspiratory efforts and improve the response.
- Supplemental oxygen
- Acetazolamide (Diamox) reduces the respiratory alkalosis and hypocapnia that can trigger central apneas by inhibiting carbonic anhydrase, thereby facilitating bicarbonate diuresis.

Hypersomnias not due to breathing disorders

Narcolepsy

Narcolepsy is a neurological disorder characterized by excessive daytime sleepiness, cataplexy (loss of muscle strength, often with falling, during periods of high emotion such as laughter), hypnagogic hallucinations (vivid dreams at sleep onset), sleep paralysis (loss of muscle strength at sleep onset or upon awakening).

Epidemiology

- Prevalence is estimated between 2 and 10 per 10,000 in the white populations of North America and Europe.
- Most common age of onset is between 12 and 30 years, with a second peak around 40 years; in 70%–80% of cases symptoms begin before age 25 years.
- Men and women equally affected

Genetics and pathophysiology

- *HLA DQB1*0602* and *HLA DQA1*0102* are narcolepsy susceptibility genes.
- Most cases are sporadic.
- Loss of hypocretin-orexin (secreted by the lateral hypothalamus, important in maintaining wakefulness) with consequent stimulation of the locus ceruleus may be important for the manifestations of narcolepsy; absence of hypocretin-orexin-secreting neurons has been demonstrated in brains from patients with narcolepsy.

Clinical features

- Excessive daytime sleepiness—usually the first symptom and most troublesome; inability to obtain relief with any amount of sleep
- Sleep attacks—sudden periods of irresistible daytime sleepiness; episodes occur during daytime, without warning; usually brief
- Cataplexy—brief episodes of bilateral weakness brought on by high emotions (laughter, anger, excitement, surprise, shock); a symptom specific for narcolepsy, but only occurs in about 70% of cases; no associated altered consciousness
- Sleep paralysis—inability to move while still awake at sleep onset (hypnagogic) or on awakening (hypnopompic)
- Hypnagogic and hypnopompic hallucinations—frightening illusions or hallucinations; may include visual imagery or auditory hallucinations
- Nocturnal sleep disruption—sleep fragmentation
- Primary narcolepsy—normal neurologic examination
- Secondary narcolepsy—may occur in patients with multiple sclerosis, stroke, head trauma, brain tumors, CNS infections

Diagnostic evaluation

- History of daytime sleepiness (daily lapses into sleep for at least 3 months) and unequivocal cataplexy
- Nocturnal sleep study (polysomnography, PSG) and multiple sleep latency test (MSLT), to rule out other sleep disorders and demonstrate either short nocturnal REM latency (<20 minutes) on PSG or a mean sleep latency less than 5 minutes and two or more naps with sleep-onset REM periods (SOREMPs) on the MSLT

Treatment

- Symptom oriented
- Sleepiness—pharmacologic-stimulant drugs: Modafinil (Provigil), Methylphenidate (Ritalin), amphetamines

- Nonpharmacologic—good sleep hygiene, adequate sleep, daytime naps
- Cataplexy—serotonin reuptake blockers (Fluoxetine), tricyclic antidepressants (Imipramine, Clomipramine), Carbamazepine (Tegretol), Gamma-hydroxybutyrate (Sodium Oxybate, Xyren)

Recurrent hypersomnia (Kleine-Levin Syndrome)

A rare syndrome characterized by the following:

- Recurrent episodes of prolonged sleep associated with hyperphagia
- Episodes may last up to several weeks and recur at irregular intervals of approximately several months.
- Disorientation, automatic behavior, sexual disinhibition, depression, hallucinations (visual or auditory), irritability, aggression often accompany the episodes of hypersomnia
- More common in boys than girls (ratio 4:1)
- Onset is typically during adolescence.
- Episodes improve in frequency and severity with age.

Treatment

- Symptomatic treatment with stimulants may offer limited benefit.
- Lithium or carbamazepine may reduce the frequency of subsequent episodes.

Idiopathic hypersomnia

Clinical features

- Excessive daytime sleepiness despite adequate sleep and excluding disorders that cause daytime sleepiness (narcolepsy, obstructive sleep apnea, periodic limb movement disorder)
- No associated REM abnormalities or cataplexy
- Often begins in adolescence
- Some patients report difficulty waking with/without disorientation ("sleep drunkenness").
- Naps are not refreshing.
- PSG shows normal or increased amount of sleep; however, REM latency is not decreased.
- MSLT reveals excessive daytime sleepiness, with a mean sleep latency of 10 minutes, but less than two SOREMPs in five naps.

Treatment

Stimulant medications offer limited benefit; patients are encouraged to maintain a regular sleep–wake schedule and avoid reductions in sleep time.

Parasomnias

Parasomnias are a group of disorders characterized by undesirable physical and mental phenomena that occur mainly or exclusively during sleep.

Classification

- Disorders of arousal: confusional arousals, sleepwalking, sleep terrors
- Sleep–wake transition disorders: sleep talking, rhythmic movement disorder, nocturnal leg cramps

- Parasomnias usually associated with REM sleep: REM sleep behavior disorder, nightmares, sleep paralysis
- Other parasomnias, with no clear relationship to a particular stage of sleep: sleep bruxism, nocturnal paroxysmal dystonia

Arousal disorders

Clinical features

- More common in children
- Events occur as partial arousals from slow-wave sleep (deeper stages of NREM sleep).
- Patients have no recollection of the events.
- Tend to improve with age

Treatment

- Sleep hygiene with maintaining regular sleep habits; avoiding sleep deprivation is recommended for confusional arousals
- Short course, up to 6 months, of a low dose of benzodiazepine, is beneficial for patients with sleepwalking and excessively disruptive behavior.

Confusional arousals

- Sudden arousal from sleep associated with disorientation and complex behaviors but low levels of motor, emotional, autonomic activation
- Episodes last seconds to minutes, occasionally up to 10 minutes or more
- Most common during first third of the night

Sleepwalking

- Complex automatisms during sleep classically associated with getting out of bed and walking, leave or attempt to leave home, opening and closing doors, climbing stairs, preparing food
- More complex motor activity but little autonomic or emotional activation
- Episodes may last a few minutes up to 30 minutes.
- Injury during the episode is the most serious complication.
- Occasionally violent behaviors may accompany the complex activity, sometimes directed at the person trying to awaken the sleepwalker.

Sleep terrors

- Pronounced autonomic and emotional activation and varying degrees of motor activity
- Episodes arise abruptly from sleep with agitation and apparent fear or terror; patient is unresponsive or only partially responsive and inconsolable.
- Prototypical episodes start with screaming and agitated behavior.
- Events are common among children aged 4 to 10 years; occur out of slow-wave sleep during first third of the night.

Sleep–wake transition disorders

- Occur during transitions between sleep and wakefulness
- Usually occur in otherwise healthy persons; are considered normal events unless their frequency or severity leads to anxiety, injuries

- Rhythmic movement disorder—also called head banging, head rolling, body rocking, is most common in infants and less common by age 4 years; tends to be more common in patients with mental retardation
- Sleeptalking—vast majority of episodes occur during arousals from NREM sleep; is common with REM behavior disorder
- Leg cramps are common in elderly and consist of a painful muscle contraction that involves the calf or foot and associated with bulging and palpable tightness of the muscle.
  - Predisposing factors include prior exercise, fluid and electrolyte disturbances, pregnancy, diabetes mellitus, nicotine and caffeine use
  - If treatment is indicated, quinine, vitamin E, verapamil ,or procainamide may be effective

Parasomnias usually associated with REM sleep

REM sleep behavior disorder

- Clinical features
  - Loss of the normal muscle REM sleep atonia associated with dream enacting behavior
  - Limb and body movements are often violent
  - Since episodes occur during REM sleep they are more frequent during the latter half of the night and usually last from a few seconds to 20 to 30 minutes
  - Serious injury to the patient or the bed partner has been described
  - Primarily a disorder of older persons, often with onset of symptoms after age 50 years
  - Some patients with RBD later develop Parkinson disease
  - PSG with video recording is useful in confirming the diagnosis

Treatment

- Clonazepam is effective in nearly 90% of cases
- Other options include imipramine, melatonin, diazepam, donepezil

Circadian rhythm sleep disorders

Clinical features

- Defined as disturbances in the natural rhythm of circadian functions
- The suprachiasmatic (SCN) nucleus of the hypothalamus is the major source of circadian rhythmicity; it synchronizes body functions with the environmental light–dark cycle.
- Melatonin, secreted by the pineal gland only during darkness, synchronizes the SCN to the environment.
- Circadian cycles are approximately 1 day in duration.
- Numerous human physiologic functions have circadian rhythmicity, including body temperature, sleep and wakefulness, plasma and urine hormones, rest and activity.
- The rhythm of sleep and wakefulness is coupled to endogenous pacemaker, such as the temperature rhythm; sleepiness is greatest during early morning hours, when the core body temperature is at a

minimum and during the afternoon hours, when body temperature is high.
- Disorders of the circadian sleep–wake cycle may be transient or persistent.

Transient disorders

Jet lag syndrome
- Clinical features
  - Arises from discordance between patient's internal circadian pacemaker and external clock time secondary to rapid travel across several time zones
  - Symptoms include difficulty falling asleep, difficulty maintaining sleep, and excessive sleepiness during the new daytime.
  - Symptoms tend to be more severe with eastbound flights, as patients find it easier to delay the time of sleep onset.
  - Tends to worsen with increasing age
- Treatment
  - Options include behavioral and scheduling changes, timed daylight exposure, short-acting hypnotics, melatonin

Shift-work sleep disorder
- Clinical features
  - Night-shift and rotating-shift work often lead to sleep problems.
  - Symptoms include daytime insomnia with short or disrupted daytime sleep, sleepiness at work, and excessive sleepiness commuting to and from work and while at work.
- Treatment
  - A sleep schedule that allows patient to obtain restful sleep 7 days or nights per week
  - Melatonin may be helpful.
  - Change to a permanent day shift may be required

Persistent disorders

Delayed-sleep-phase syndrome
- Timing of sleep onset is delayed relative to clock time, resulting in waking up late in the morning
- Difficulty awakening and getting up in the morning is the usual presenting complaint.
- Patients tend to fall asleep late, anytime between 1 am and 6 am.
- When sleep is undisturbed, the sleep period is of normal length.
- Chronotherapy (progressive delay in time of sleep onset) is the traditional treatment.
- Bright light therapy and exercise in the morning may help.

Advanced-sleep-phase syndrome
- Characterized by early sleep onset (6 to 8 pm) and early morning wake time (1 and 3 am)
- More frequent in the elderly
- Exacerbated by naps during the day and early morning walks
- Exposure to bright light and mild activity in the evening may delay the bedtime

Irregular sleep–wake pattern disorder
- Complaints of insomnia or excessive daytime sleepiness
- One or more sleep episodes in a 24-hour period
- Pattern must have been present for 3 months
- Personality disorder or blindness may be predisposing factors; often patients have congenital, developmental, or degenerative brain dysfunction

Non-24-hour sleep–wake disorder
- Internal pacemaker is not entrained to the 24-hour day–night cycle and runs based on a shorter or longer period.
- Progressive delays in sleep and wake times
- Most individuals are blind, with loss of retinal input to the SCN as a cause of the syndrome; absence of light input runs with a rhythm that is longer than 24 hours (up to 27 hours).
- Management is difficult; strict 24-hour scheduling of sleep and awake activities may have some benefit.

Sleep-related movement disorders

Restless legs syndrome (RLS)

Clinical features
- Paresthesias (abnormal sensations) and dysesthesias (uncomfortable sensations) in the legs and sometimes the arms, worse at rest, in the evening or at night, and associated with an urge to move (motor restlessness)
- Mean age of onset is in the middle age
- Sleep disturbances: difficulty initiating or maintaining sleep, excessive daytime sleepiness (less often)
- Involuntary movements during wake or sleep (periodic leg movements in sleep, PLMS) in up to 80%–90% of patients
- Primary RLS: normal neurologic examination; possible abnormality in iron transport into the CNS or in use of iron as it relates to dopaminergic neurons
- Secondary RLS: end-stage renal failure, pregnancy, iron deficiency, certain drugs
- Some familial cases are related to deficiencies in iron transporter proteins.

Diagnostic evaluation
- Diagnosis is usually made on clinical grounds.
- Complete blood count, serum iron, total iron-binding capacity, serum ferritin levels, blood urea nitrogen, creatinine should be checked to rule out treatable causes

- PSG has limited value, as PLMs are common in persons without RLS, and about 10%–20% of persons with RLS do not have PLMs.

Treatment

- Dopamine agonists: Ropinirole, Pramipexole, Pergolide, at smaller doses than used for Parkinson disease
- Gabapentin—useful to treat the discomfort and movement at night
- Other anticonvulsant medications, such as Carbamazepine, Zonisamide, Topiramate, and Benzodiazepines
- For patients with low serum iron, iron supplementation should be considered.

Periodic limb movements of sleep (PLMS)

Clinical features

- Characterized as repetitive stereotyped dorsiflexions of the big toe with fanning of the small toes, accompanied by flexion of the ankles, knees and thighs that typically recur at intervals of 5–90 seconds with a duration of 0.5–5 seconds
- Four movements must be counted per episode to meet the polysomnographic criteria of PLMS
- Most common in NREM sleep, stages 1 and 2
- Periodic leg movement disorder (PLMD)
  - Characterized by the syndrome of leg movements and insomnia or excessive daytime sleepiness
  - Severity of symptoms is related to the frequency of limb movements and associated arousals or awakenings
  - Associated with uremia, peripheral vascular disease, anemia, arthritis, peripheral neuropathy, spinal cord lesions, caffeine use, antidepressants
  - Many patients with PLMS do not have RLS.

Diagnostic evaluation

- PLM index is the number of leg movements per hour.
- PLM index must be >5/hr; for a leg movement to be counted as a PLM, it must occur in a sequence of at least four leg movements separated by 5–90 seconds.
- PLMD consists of PLMS and symptoms of insomnia or daytime sleepiness
- PLMS may be seen in association with narcolepsy, OSA, CPAP titration

Treatment

- Should be considered only if the PLMS and associated sleep disturbance appear to be responsible
- Most helpful treatments for PLMs are those used for RLS

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Chapter 11

Infectious and inflammatory conditions

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Infectious disease: bacterial meningitis

Incidence and microbiology Annual incidence around 2–3/100,000 with peaks in infants and adolescents. Vaccination against Haemophilus influenzae type b and group C meningococcus has had significant impact.

Common meningitides by age

- Newborns: Group B *Streptococcus*, *Listeria monocytogenes*, *E. coli*
- Infants (<6 months): *Listeria*, *S. pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b
- Adolescence through middle age: *S. pneumoniae*, *Neisseria*, *Haemophilus*
- Elderly: *S. pneumoniae*, *Neisseria*, *Listeria*

Acquired risk factors

- Splenic dysfunction or splenectomy (*Streptococcus pneumoniae*)
- T lymphocyte defects due to chemotherapy, malignancy, HIV (*Listeria monocytogenes*)
- Sickle cell disease (*Staphylococcus*)
- Skull fracture, middle and inner ear fistulas (*S. pneumoniae*)
- Penetrating skull trauma, CSF shunts (*Staphylococcus*)
- Mucosal epithelial damage, e.g., smoking, recent viral illness
- Consider tuberculous meningitis in those from endemic areas
- In the immunosuppressed, e.g., HIV—cryptococcal meningitis and tuberculous meningitis
- Crowded living conditions, e.g., college dorms, military barracks (*Neisseria*)

Clinical features

Presenting features typically with some combination of headache, fever, photophobia, and neck stiffness. In addition:

- Cranial nerve palsies (III, IV, VI, VII)
- Focal neurological deficits
- Seizures (20%–30%). Usually in *S. pneumoniae* and *H. influenzae* meningitis
- Increased ICP (altered consciousness level, hypertension, bradycardia, abnormal respiratory pattern, papilledema [late])
- Purpura or petechial hemorrhages (nonblanching with glass test): *Neisseria meningitidis*
- Septic shock: *N. meningitidis*
- Tuberculous meningitis may be more insidious with gradual development of fever, weight loss, headache with progression to focal deficit, altered consciousness
- Look for evidence of immunosuppression as may be the first presentation of HIV or lymphoproliferative disorder, e.g., oral candidiasis, lymphadenopathy

Investigations

1. Blood culture as latex agglutination bacterial antigen tests or PCR can be performed and may remain positive even after antibiotics.
2. CXR for evidence of TB
3. CT scan does *not* exclude raised ICP. Often normal in appearance. Occasionally with mild ventricular dilatation or widening of subarachnoid space
4. Lumbar puncture (best obtained prior to or within 4 hours of starting antibiotic therapy) is contraindicated if
   - Signs of increased ICP
   - Decreased Glasgow Coma Scale
   - Coagulopathy (increased PT/INR or PTT, platelets<50,000)
   - Focal symptoms, signs or seizures (unless CT scan normal)
   - Cardiovascular compromise (medical instability)
   - Infection of skin at LP site
5. See Table 11.1 for lumbar puncture and blood findings in different forms of meningitis
6. MRI findings commonly include meningeal enhancement and enhancing subarachnoid exudates deep in sulci (see Fig. 11.1).

Management

Choice of antibiotic

Choice of antibiotic depends on age of patient and any other associated features, e.g., immunocompromised. *CT or LP should not delay first dose of antibiotic.*

In adults likely organisms are as follows:

- *Streptococcus pneumoniae*
- Neisseria meningitides
- If >60 years, Listeria monocytogenes

Table 11.1 LP findings in meningitis

Condition	CSF pressure (cmH2O)	WBC (u/L)	Protein (mg/L)	Glucose (mmol/L)
Normal	5–20	<5 lymphocytes	15–45	70% blood glucose
Bacterial meningitis	Increased	100–60 000, mainly neutrophils	50–500	<40% blood glucose
Tuberculous meningitis	Increased	10–500, neutrophils in early disease, lymphocytes later	50–500	Decreased <40% of blood glucose
Fungal meningitis	Increased	25–500, mainly lymphocytes	50–500	Decreased
Viral meningitis	Normal or increased	Increased lymphocytes	50–200	Normal

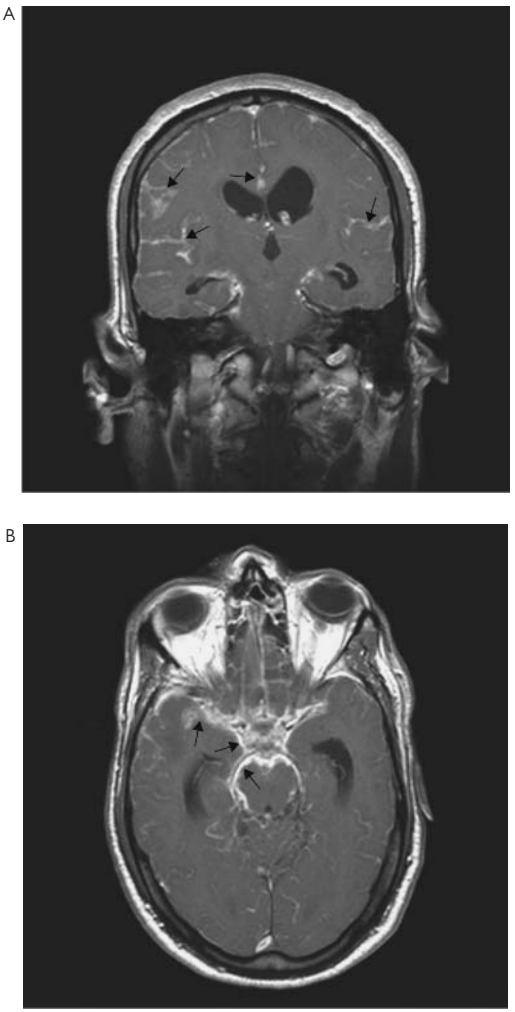

Figure 11.1 Meningitis. (A) Postcontrast coronal MRI. Pneumococcal meningitis: thickening and enhancement of leptomeningeal surfaces over cerebral hemispheres and Sylvian fissure (black arrows). (B) Postcontrast axial MRI. Tuberculous meningitis: thickening and enhancement of basal meninges in suprachiasmatic and prepontine cisterns (black arrows). Note in both cases there is dilation of the ventricles due to communicating hydrocephalus.

Empiric therapy (see Table 11.2 for dosage recommendations)

- Adults 18–60 (otherwise healthy and in the community)
  - Ceftriaxone or cefotaxime PLUS
  - Vancomycin in suspected *S. pneumoniae* until sensitivities are known in case of resistance
- Adults 60 + (otherwise healthy and in community)
  - As for adults 18–60 years old, PLUS
  - Ampicillin to cover Listeria
- Adults with nosocomial meningitis
  - Ceftazidime—less CNS penetration than ceftriaxone but covers gram-negative bacilli and Pseudomonas, PLUS
  - Vancomycin in suspected *S. pneumoniae* until sensitivities are known in case of resistance
- Adults—immunocompromised
  - As for adults with nosocomial meningitis above, PLUS
  - Ampicillin to cover Listeria

If clear history of beta lactam anaphylaxis:

- Chloramphenicol may be substituted for beta-lactam, PLUS
- Vancomycin
- If >50 years, add trimethoprim-sulfamethoxazole or meropenem in place of ampicillin to cover Listeria

Table 11.2 Recommended dosages of IV antibiotics for treating acute bacterial meningitis and tuberculous meningitis

Ampicillin	2 g q4hr or 50 mg/kg q6hr
Cefotaxime	2g q6hr
Ceftazidime	2 g q8hr
Ceftriaxone	2 g q12hr
Chloramphenicol	25 mg/kg q6hr
Ethambutol	15–25 mg/kg daily
Gentamicin	1–2 mg/kg q8hr
Isoniazid	5 mg/kg/day
Linezolid	600 mg q12hr
Meropenem	6 g q8hr
Nafcillin	2 g q4hr
Oxacillin	2 g q4hr
Penicillin G	4 million units q4hr
Pyrazinamide	15–30 mg/kg/day
Rifampin	10 mg/kg/day
Trimethoprim-sulfamethoxazole	10–20 mg/kg divided q6–12hr
Vancomycin	1 g q12hr or 500 mg q6hr

Therapy after identification by class of bacteria or specific organism from CSF or blood. (See Table 11.2 for dosage recommendation.)

- Gram or AFB stain
  - Gram-positive cocci: ceftriaxone (or cefotaxime) PLUS vancomycin
  - Gram-negative cocci: Penicillin G or if *H. influenzae* suspected (small pleomorphic rods), ceftriaxone (or cefotaxime)
  - Gram-positive bacilli: ampicillin PLUS gentamicin
  - Gram-negative bacilli: ceftriaxone (or cefotaxime) PLUS gentamicin (Note: ceftazidime is preferred in place of ceftriaxone if recent neurosurgical procedure or head trauma)
  - AFB-positive: Start 4 drug regimen for tuberculosis. Place patient in negative pressure respiratory isolation room. Assess for pulmonary and/or disseminated disease
- Cultured organism
- *N. meningitidis*
  - Ceftriaxone (or cefotaxime)
- *S. pneumoniae*
  - Ceftriaxone (or cefotaxime)
  - Add vancomycin if patient from area of cephalosporin/penicillin resistance
- *H. influenzae:* ceftriaxone (or cefotaxime) if beta-lactamase positive; ampicillin if beta-lactamase negative
- *L. monocytogenes*: ampicillin + gentamicin
- Group B *Streptococcus*: Penicillin G
- E. coli and Enterobacteriaceae in general: ceftriaxone (or cefotaxime) PLUS gentamicin
- Enterococcus: ampicillin PLUS gentamicin; if ampicillin resistant, then vancomycin PLUS gentamicin; if vancomycin and ampicillin resistant, then linezolid
- Staph aureus: if methicillin sensitive, then nafcillin or oxacillin; if methicillin resistant, then vancomycin
- Staph epidermidis: vancomycin
- Pseudomonas or Acetinobacter: ceftazidime PLUS gentamicin
- Tuberculosis meningitis: 4-drug therapy (isoniazid, rifampin, pyrazinamide, ethambutol). Note: Pyridoxine given prophylactically (25–100 mg daily) can minimize risk of peripheral neuropathy due to isoniazid

Increased ICP

- *A medical emergency*. Patient should be managed in ICU. Interventions may include elevation of head of bed to 30 degrees, neutral head position, IV mannitol administration, sedation, intubation and hyperventilation, placement of ventriculostomy, and controlled hypothermia.

Seizures

- Should be treated initially with lorazepam 0.1 mg/kg IV (in divided doses, usually starting with 2 mg), followed by IV phenytoin 20 mg/kg as a loading dose under ECG monitoring followed by maintenance dose IV of 5 mg/kg/day. If seizures continue, treat as for status epilepticus.

Corticosteroids (dexamethasone)

- Shown to reduce morbidity in adults specifically in *S. pneumoniae* and tuberculous meningitis. Data do not include meningococcal meningitis, but it is reasonable to consider at least until organism isolated—10 mg dexamethasone 6-hourly IV for 4 days with first dose given prior to or with first antibiotic dose
- Shown to reduce morbidity (hearing loss and focal neurological deficits) in children, specifically in those with *H. influenzae* type b. Data are unclear as to whether there may also be benefit in children with pneumococcal meningitis. If used, the first dose of dexamethasone (0.15 mg/kg q6hr over 2–4 days) *must* be given prior to or at the same time as administration of first dose of antibiotics; delay by even 1 hour results in lost benefit.

Bacterial infections and toxins

Subdural infections

- Relatively rare infection with collections of pus between dura and arachnoid meningeal layers
- Direct extension of infection from meninges, sinuses, middle ear or as complication of skull fracture
- Streptococcus is the most frequent organism.
- Symptoms include focal neurological deficits, meningismus, chills, fever, headache, and confusion evolving over hours to days.
- Avoid lumbar puncture due to risk of herniation; if done, findings include increased ICP, mild pleocytosis (polymorph or lymphocyte predominant), increased protein, sterile CSF
- Treatment
  - Surgical evacuation of empyema
  - Antibiotics appropriate to suspected or cultured organism

Epidural infections

Intracranial epidural abscess

- Associated with infection in overlying cranial bones
  - Extension of infection from sinuses, mastoid space, middle ear, meninges, or as a result of septicemia
  - Streptococcus most common pathogen (Staphylococcus and gram-negative bacteria also isolated frequently)
- Patient appears ill with headache and fever, but rarely has focal neurological findings
- Diagnosis by CT or MRI
- Treatment
  - Surgical evacuation of empyema
  - Antibiotics appropriate to suspected or cultured organism

Spinal epidural abscess

- Three routes of infection:
  - Direct extension of infection from adjacent tissues

  - Hematogenous spread
  - Penetration or seeding from a procedure
- *S. aureus* most common pathogen (50%–60%)
- Midthoracic level most frequently affected
- Symptoms and signs
  - Severe back pain
  - Headache, fever, malaise
  - Paresis of lower extremities
  - Meningismus
  - Percussion tenderness over the spine
- Diagnosis by CT or MRI
- Avoid lumbar puncture due to risk of herniation; if done, findings include increased ICP, mild pleocytosis (polymorph or lymphocyte predominant), increased protein, sterile CSF
- Treatment
  - Surgical evacuation
  - Antibiotics appropriate to suspected or cultured organism

Bacterial endocarditis

- Etiological predisposition to infected cardiac valves
  - Rheumatic fever
  - Prosthetic valves
  - Intravenous drug use
  - Congenital cardiac abnormalities
- Cerebral complications—ultimately related to infective emboli
  - Embolic infarcts
  - Brain abscess
  - Meningitis
  - Mycotic aneurysms
  - Hemorrhage secondary to any of above complications
- Associated signs and symptoms can include fever, weight loss, malaise, seizures
- Diagnostic procedures:
  - CT or MRI
  - Angiography
  - Lumbar puncture
  - Blood cultures
  - Complete blood count
- Treatment:
  - Antibiotics for cardiac infection and/or brain abscess
  - Cardiac valve replacement may be indicated
  - Surgical drainage of brain abscess may be required
  - Avoid anticoagulation in setting of embolic brain infarcts or mycotic aneurysms

Other bacterial infections with neurological sequelae

Spirochete infections

Syphilis (Treponema pallidum)

- Organism or immune reaction to organism promotes inflammatory infiltration of meninges, blood vessels, and eventually brain parenchyma with variable necrosis or demyelination at any level of the neuraxis
- Early syndromes: fever, meningismus, headache, brain infarction, myelitis, cranial nerve palsies (see Table 11.3)
- Late syndromes: meningovascular disease; dementia +/− seizures; tabes dorsalis (see Table 11.3)
- Pathognomic examination finding: Argyll-Robertson pupils—small irregular pupils that react to accommodation but not to light

Table 11.3 Syphilitic syndromes

Syndrome	Lab/imaging	Clinical symptoms
Asymptomatic	Meningeal enhancement on MRI	No clinical symptoms
Meningeal (within 1 year of primary infection)	Meningeal enhancement, meningitis, hydrocephalus, cerebral infarction, increased ICP	Cranial nerve palsies, focal deficits related to infarction or increased intracranial pressure
Cerebrovascular (5–30 years after primary infection	Meningeal enhancement, cerebral infarction	Headache, focal deficits related to infarction
Meningovascular syphilis of the spinal cord	Transverse myelitis, subacute amyotrophy (rarely)	Focal deficits, spasticity, bladder dysfunction, or flaccid weakness
Gumma	Avascular granuloma attached to dura (localized meningeal syphilis)	Associated with more widespread meningeal disease and referable symptoms
Syphilitic meningoencephalitis (late presentation)	Thickened meninges, sulcal atrophy, granular ependymitis of ventricles	Dementia, poor judgment, emotional lability, quadriparesis, seizures
Tabes dorsalis (late presentation)		Ataxia, lancinating leg pains, sphincter dysfunction, muscle atrophy, optic atrophy, Charcot joints
Congenital neurosyphilis (passed from mother to child between months 4–7 of gestation)	Hydrocephalus	Hutchinson triad: interstitial keratitis, deformed teeth, hearing loss
General paresis of the insane		Dementia

- Prevalence increasing in persons infected with HIV
- Diagnosis: serum VDRL or RPR confirmed by fluorescent treponemal antibody test (FTA), CSF, and VDRL.
- Treatment: Penicillin G, various regimens, alternatives for penicillin-allergic patients include doxycycline. Probenicid may be added for patients with optic and auditory involvement.

Leptospirosis (Leptospira)

- Transmission through contact with infected animals or contaminated environment—entry through broken epidermal barrier
- Symptoms occur 1–2 weeks after infection
  - Aseptic meningitis with fever, chills, myalgia, headache, confusion
  - Encephalitis, intracerebral hemorrhage, myelitis, optic neuritis
  - Mononeuritis or acute peripheral nerve demyelination (rarely)
- Clinical findings may include lymphadenopathy, hepatosplenomegaly, rash
- Lab/Imaging findings
  - MRI: normal or enhancing cortical/subcortical lesions
  - LP: normal or mild pleocytosis—neutrophils and monocytes
  - Labs: elevated LFTS, increased ESR, UA with proteinuria, hematuria, and pyuria
- Diagnosis: serological studies: IgM antibody detection
- Treatment: high-dose penicillin or doxycycline

Lyme disease (Borrelia burgdorferi)

- Transmission through tick bite
- Three stages
  - Stage I (up to 30 days): bulls-eye rash (erythema chronicum migrans, headache, myalgia, cranial nerve palsies [VII particularly])
  - Stage II (several weeks to months): meningeal signs, radiculitis with severe pain or weakness (focal or generalized), cranial nerve palsies (VII particularly), irritability
  - Stage III (months to years): encephalopathy, myelopathy, polyneuropathy (primarily sensory), arthropathy
- Lab findings: LP—elevated protein and WBCs, positive O-bands
- Diagnosis: serological testing; care must be taken in interpretation as there are many cross-reacting antigens to confuse results
- Treatment: doxycycline + amoxicillin; alternative regimen: cefuroxime or erythromycin

Whipple disease (Tropheryma whippelii)

- Originally described as a GI disease associated with arthralgias
- Weight loss, abdominal pain, diarrhea, arthralgia, mild fever, lymphadenopathy, anemia, hypoalbuminemia
- Neurological manifestations
  - Cognitive changes
  - Supranuclear gaze palsy (vertical > horizontal)
  - Psychiatric signs
  - Spasticity/brisk reflexes
  - Cranial nerve abnormalities
  - Myoclonus
  - Seizures

- Ataxia
- Diagnosis: by intestinal biopsy to demonstrate macrophage collections and by PCR or electron microscopy to demonstrate presence of the organism
- Treatment: ceftriaxone (2 gm IV bid) for 14–30 days, then Bactrim DS (160/800 mg po bid) or cefixime (400 mg daily) for 1 year; other agents. Tetracycline and penicillin have also been used with success.

Leprosy (Mycobacterium leprae)

- Common in tropical and subtropical areas
- Transmitted by direct contact
- Tuberculoid (paucibacillary) and lepromatous (multibacillary) forms
- Predilection for peripheral nerves resulting in thickened nerves with overgrowth of connective tissue and axonal loss—most common with tuberculoid form
- Attacks of neuropathic pain, weakness, or sensory loss
- Nerves closest to the skin surface (coolest nerves) are preferentially affected
  - Weakness and atrophy seen most commonly in hand and foot intrinsic muscles; deep nerves and proximal muscles spared
  - Cutaneous sensory loss prominent with preservation of deeper sensory structures
- Beware false-positive test for syphilis—seen in one third
- Treatment with dapsone (50–100 mg daily) and rifampin (600 mg monthly) for tuberculoid form: dapsone and rifampin and clofazimine (50 mg daily) for lepromatous form

Rickettsial infections: Rocky Mountain spotted fever, typhus (three types), Ehrlichiosis

- Transmitted by bite of arthropod
  - Rocky Mountain spotted fever: tick
  - Typhus: lice, chiggers, and fleas
  - Ehrlichiosis: tick
- Febrile illness associated with mental status changes
- CNS parenchymal and vascular involvement
  - Rocky Mountain spotted fever: brain edema, petechial hemorrhages, thrombosis of small arterioles
  - Typhus: thrombosis of cerebral arteries
- Treatment: doxycycline, tetracycline, or chloramphenicol

Brucellosis (Brucella)

- Undulant fever transmitted by cattle or swine or by ingestion of unpasteurized milk products
- Symptoms and signs can include headache, meningitis, brain abscesses, cranial nerve palsies, optic neuritis, and peripheral neuropathy.
- Treatment: doxycycline or trimethoprim-sulfamethoxazole, *plus* an aminoglycoside

Mycoplasma infection (Mycoplasma pneumoniae)

- Major cause of pneumonia
- Transmitted by inhalation
- Less often can be associated with meningitis, encephalitis, cerebellar ataxia, transverse myelitis, radiculopathies, cranial nerve palsies
- Treatment: doxycycline or erythromycin

Legionella pneumophila

- Pneumonia most common
- Transmitted by inhalation
- Uncommon neurological symptoms may include encephalitis, cerebellar ataxia, chorea, and peripheral neuropathy
- Treatment: azithromycin or erythromycin

Bacterial toxins

Diphtheria (Corynebacterium diphtheriae)

- Exotoxin has tropism for peripheral nerve with demyelinating peripheral neuropathy manifested in 20% of patients
  - Also tropism for cardiac muscle resulting in myocarditis
- Descending paralysis:
  - Impaired visual accommodation, then
  - Ocular and oropharyngeal muscle paresis, then
  - Limb weakness that may progress to quadriparesis

Botulism (Clostridia botulinum)— botulinum toxin

- Ingestion of toxin-contaminated food (adults); ingestion of bacteria (infants) with subsequent toxin production; wound contamination
- Toxin absorbed from GI tract (or wound), then spread hematogenously; symptoms occur 6–48 hours after ingestion—or later in case of infants where bacteria grow in digestive tract and produce toxin
- Toxin impairs release of acetylcholine at peripheral presynaptic nerve ending through interference with fusion of presynaptic acetylcholine-containing vesicles
  - Descending weakness of striated and smooth muscles
  - Autonomic dysfunction
- Typical presentation (with symptom progression):
  - Possible nausea, vomiting, diarrhea (not always present)
  - Loss of convergence of eyes
  - Ptosis, ophthalmoplegia, dilated or unreactive pupils
  - Dysphagia, dysarthria
  - Weakness of limbs in descending pattern
  - Constipation and urinary retention may be present
  - If undiagnosed, convulsions and coma with cardiac or respiratory failure may result (within 4–8 days, if large amount of toxin ingested)

- Diagnosis
  - History, clinical suspicion
  - Testing of contaminated food or feces of patient for toxin
  - Nerve conduction studies supportive
- Treatment
  - Botulinum antitoxin
  - Supportive care

Tetanus (Clostridia tetani)—*tetanospasmin toxin*

- Bacterial spores ubiquitous in environment and enter body through disrupted skin barrier (puncture or wound)
- Necrotic tissue required for germination of spores and subsequent production of toxin, which is spread hematogenously
- Toxin impairs release of acetylcholine at presynaptic nerve ending through interference with fusion of presynaptic vesicles
  - Tropism for inhibitory neurons in CNS, resulting in decreased release of GABA and glycine → central hyperexcitability
  - Can affect autonomic function
  - Central effects predominate over peripheral effects
- Symptoms present from 3 days to 3 weeks after injection
  - Generalized tetanus
  - Facial muscle stiffness: trismus, risus sardonicus,
  - Muscle stiffness and rigidity of back (opisthotonos)
  - Paroxysmal muscle spasms with minimal or no trigger
  - Localized tetanus
  - Rare—seen in previously immunized persons
  - Muscle stiffness and spasms limited to area of entry of spores
- Diagnosis
  - Characteristic signs and history of wound
- Treatment
  - Debride wound
  - Antitoxin to neutralize toxin not yet bound to nerves
  - Supportive care in ICU—may require respiratory support, benzodiazepines, or neuromuscular blockade

Viral meningoencephalitis

Infection of the brain parenchyma is usually accompanied by a meningitis producing a meningoencephalitis. The organism is identified in only 30%–50% of cases.

Incidence

- Herpes simplex encephalitis (HSV-1), most frequent cause of sporadic fatal encephalitis: 1 case per million per year probably an underestimate. Currently the only pharmacologically treatable encephalitide
- In the Far East, Japanese B encephalitis causes 15,000 deaths/year.

Etiology (See Table 11.4)

Table 11.4 Etiology of viral encephalitis

Worldwide distribution	Geographically specific
HSV -1 and 2	Western equine virus
EBV	Eastern equine virus
CMV	California encephalitis
VZV	St Louis encephalitis
HHV6	Japanese B encephalitis
Non-polio enteroviruses	Tick-borne encephalitis
Mumps	West Nile virus
Rabies	
HIV (at seroconversion)	

Clinical features

- Essential to take a full travel history (e.g., Japanese B encephalitis)
- History of animal bites (e.g., rabies)
- No association between HSV-1 and cold sores
- Presentation, especially for HSV encephalitis, acute with
  - Headache
  - Fever
  - Focal neurological deficits (e.g., dysphasia)
  - Seizures
  - Encephalopathic presentation with confusion, delirium, behavioral changes, and coma
- If untreated, mortality (HSV): 70%
- With acyclovir, mortality is still high at 20%–30%

Imaging

- CT: normal early in course. With HSV-1, may see hypodensities in temporal lobes with mild mass effect; hemorrhage later in course
- MRI : HSV-1 (see Fig. 11.2)

Differential diagnosis

Diffuse encephalopathy

- Liver and renal failure
- Diabetic coma
- Anoxic/ischemic brain injury
- Systemic infection
- Toxic drug effects
- Mitochondrial cytopathies

Non-viral causes of infectious encephalitis

- *Mycobacterium tuberculosis*
- *Mycoplasma pneumoniae*
- *Listeria monocytogenes*

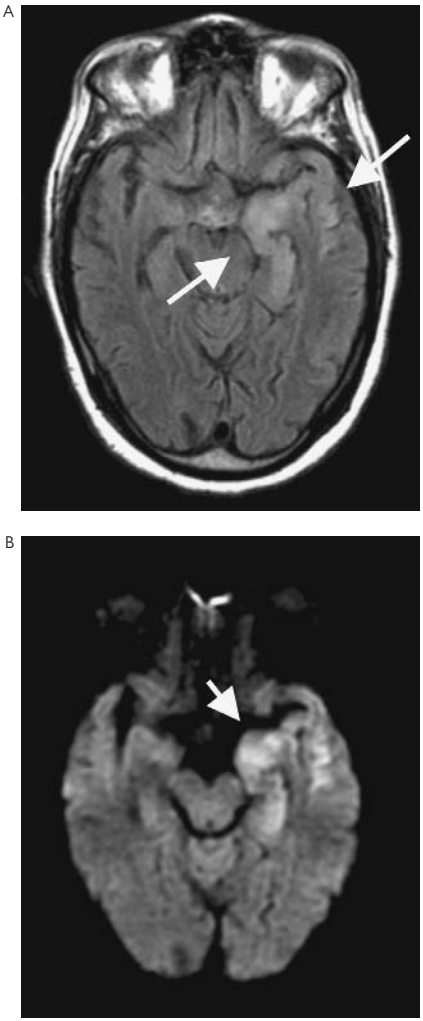

Figure 11.2 MRI: HSV encephalitis. Axial FLAIR (A) image demonstrates high signal throughout the left mesial temporal lobe and anterior temporal tip in a patient with known herpes simplex viral encephalopathy. Diffusion-weighted imaging (B) demonstrates restricted diffusion in the same location consistent with active infection.

- *Borrelia burgdorferi*
- Brucellosis
- Leptospirosis
- Legionella
- All causes of pyogenic meningitis
- Fungal: cryptococcus, aspergillosis, candidiasis
- Parasitic: human African trypanosomiasis, toxoplasmosis, schistosomiasis
- *Acute disseminated encephalitis* (ADEM) May have a similar presentation but clues include recent vaccination, spinal cord and optic nerve involvement, and widespread white matter involvement on MRI.

Investigations

- Routine blood investigations may reveal a metabolic etiology
- CXR to exclude TB, legionella, mycoplasma, and neoplasia
- Baseline virology serology may later provide evidence of recent infection
- CT/MRI: gyral swelling and signal abnormality/low attenuation, which is typically bilateral but asymmetric with hemorrhage

EEG

- Emergency EEG may be necessary to make diagnosis. Look for diffuse nonspecific abnormalities or periodic lateralizing epileptiform discharges (PLEDS)
- In H. simplex encephalitis PLEDS may be bilateral and evolve with differing periodicity over each lobe.
- If PLEDS occur away from the temporal lobe, interpret with caution.
  - May improve spontaneously and rapidly

LP

- Lymphocytic pleocytosis 10–200/mm^3
- Protein, 0.6–6 g/L
- Rarely, the CSF may be normal.
- CSF PCR to detect HSV-1 is 95% specific. Sensitivity if taken 2–10 days after onset is 95%. False-negative results are most likely in the first 48 hours and after 10 days.

Management

- Acyclovir (10 mg/kg q8hr) immediately when diagnosis is suspected. Continue for 14 days. It should only be discontinued if an alternative definite diagnosis is made. In immunosuppressed patients, treat for 21 days. Note: Renal toxicity may occur and needs to be monitored. Five percent of patients may relapse.
- Best predictors of outcome are treatment within 4 days of onset, Glasgow Coma Scale >6 at presentation
- Steroids if there is evidence of raised ICP
- Anti-epileptic drugs (AEDs) for seizures
- May need cardiac /ICU monitoring

Highlight on West Nile virus

- An arbovirus widely distributed worldwide with recently increasing outbreaks in the United States
- Peak disease incidence in late summer and fall with sporadic cases throughout the year, especially in southern climates
- Transmission primarily by mosquito bites; amplification of virus in birds
- Transmission also reported through blood transfusion, organ donation, transplacental, and through breast milk

Clinical manifestations

- Asymptomatic in up to 80%
- Self-limited febrile illness—West Nile fever
  - Fatigue, fever, headache, myalgias, nausea, vomiting, diarrhea
  - Maculopapular rash on back, chest, and arms in 50%
  - 3–10-day course
- Neuroinvasive disease
  - Meningoencephalitis—seizures common
  - Flaccid paralysis resembling poliomyelitis (affecting anterior horn cells)—can be asymmetric
  - Acute peripheral demyelinating syndrome (rare)
  - Tremor and myoclonus
  - Parkinsonian symptoms
  - Cranial nerve palsies and brachial plexopathy
  - Ataxia
  - Optic neuritis

Laboratory findings

- CBC: normal or elevated WBC
- LP: pleocytosis with lymphocytic predominance and elevated protein
- Imaging
  - CT: usually normal
  - MRI: may show enhancement of meninges and/or periventricular areas; hyperintensities in deep gray matter, brainstem, or spinal cord initially or developing within weeks
- EEG: generalized slowing, predominantly in frontotemporal region
- EMG (in acute flaccid paralysis): NCS with preserved sensory responses, decreased amplitude motor responses

Diagnosis

- IgM antibody detection by enzyme-linked immunoabsorbent assay (ELISA) – Serum or CSF
- IgM antibody may not be detected within first week of infection—repeat ELISA if clinical suspicion high
- Beware of false positives in persons with recent vaccinations

Treatment

- Supportive

Neurology of HIV/AIDS: introduction

- HIV infection can affect the whole neuraxis at all stages of the illness.
- Different pathological processes can be present simultaneously.

Basic principles

- Ten percent of patients may have a neurological disorder at seroconversion
  - Meningoencephalitis
  - Myelitis
  - Guillain-Barre syndrome (GBS)
  - Polymyositis
- Persistent CSF abnormalities, even during the asymptomatic phase, include
  - Mild pleocytosis
  - Increased protein
  - Oligoclonal bands
- To diagnose conditions such as cryptococcal meningitis, specific tests such as the cryptococcal antigen test are required.
- Decreased inflammatory response: one-third of patients with cryptococcal meningitis have meningismus
- Low threshold for brain imaging and lumbar puncture required
- Decreased antibody response: in toxoplasmosis, there is no rise in IgM levels
- CD4 count is a useful guide to the underlying pathological process
  - Toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy occur at CD4 counts < 200
  - CMV disease occurs at CD4 counts < 50

Neurological disorders due to HIV

HIV-associated dementia (HAD)

- Usually occurs late in the disease
- Symptoms include impaired attention, memory loss, and apathy.
- Signs in the early stages include jerky eye movements, brisk reflexes, and cerebellar abnormalities.
- Differential diagnoses include metabolic derangement, e.g., hypoxia, recreational drug use, and depression.

Investigations to exclude other pathology

- MRI shows atrophy and diffuse white matter changes (see Fig. 11.3).
- CSF examination (nonspecific cytochemical abnormalities)
- CSF HIV RNA load cannot be used to diagnose HAD.
- Neuropsychological assessment useful—subcortical dementia with abnormalities in the domains of information processing, psychomotor speed, and recall memory

Vacuolar myelopathy (VM)

- Occurs in conjunction with HIV dementia

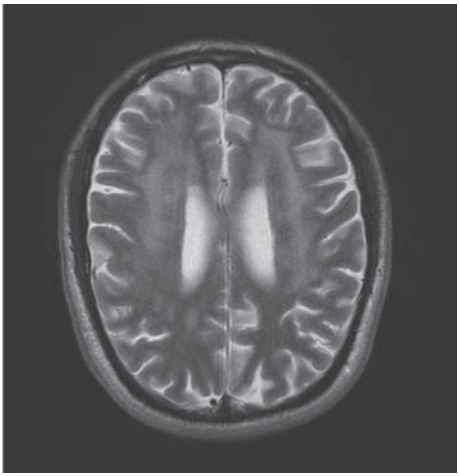

Figure 11.3 HIV encephalopathy (T2-weighted axial MRI) in young patient (20s). Bilateral hyperintensity involving the cerebral white matter in association with volume loss denoted by prominence of the cerebral sulci.

- Signs of a spastic paraparesis without a sensory level
- Resembles subacute combined degeneration due to vitamin B_{12} deficiency
- MRI usually normal
- Check B_{12} level and, if low normal, methylmalonic acid levels. If low, treat with B_{12} as monthly intramuscular injection
- Consider checking indicated HTLV-1 serology as co-infection may occur

Peripheral nerve syndromes

Distal sensory peripheral neuropathy (DSPN)

- Twenty-five percent of AIDS patients
- Occurs late in AIDS
- Symptoms of paresthesias, burning pain, dysesthesias
- Signs: little or no weakness, reduced or absent ankle reflexes. Impaired sensation to pain and temperature (mainly a small-fiber neuropathy)
- Neuropathy due to antiretroviral drugs (e.g., ddC, ddI, d4T) is very similar.
- Other drugs that may also cause neuropathy include isoniazid, vincristine, thalidomide, and metronidazole.

Investigations
- B_{12}, glucose levels, alcohol intake
- Nerve conduction studies normal or may show an axonal neuropathy
- Thermal thresholds abnormal
- Nerve biopsy unnecessary unless abnormal features such as significant weakness are present to exclude vasculitis, demyelination, or lymphoma

Other peripheral nerve syndromes
- Mononeuritis multiplex due to HIV vasculitis and CMV
- Acute and chronic demyelinating polyneuropathy
- Diffuse inflammatory lymphocytosis syndrome (DILS) resembles Sjögren syndrome. Occurs during immunocompetent phases and associated with a high CD8 count

Polyradiculopathy
- CMV
- Lymphoma
- Herpes viruses
- Syphilis

Myopathy
- Polymyositis occurs in the early stages of HIV infection
- Zidovudine causes a mitochondrial myopathy

Opportunistic infections associated with HIV

Toxoplasmosis
- Usually a reactivation in individuals who have been previously exposed and have positive toxoplasma serology
- Acute or subacute presentation with focal neurological signs or movement disorders such as athetosis and symptoms and signs of increased ICP
- Imaging: multiple focal enhancing lesions with surrounding edema (see Fig. 11.4)
- Differential diagnoses: primary CNS lymphoma, tuberculoma, or tuberculous abscesses
- Treatment: see Table 11.5
- If significant mass effect add dexamethasone 4 mg q6hr and gradually taper (see Fig. 11.5)

Cryptococcal meningitis
- Acute or subacute presentation with headache, altered mental state, and meningism
- Imaging: hydrocephalus, cryptococcomas, or dilated Virchow-Robin spaces filled with organisms
- CSF
  - Opening pressure frequently increased
  - Pleocytosis, increased protein, and decreased sugar but may be normal
  - India ink staining positive in 75%
  - Cryptococcal antigen positive in 95%

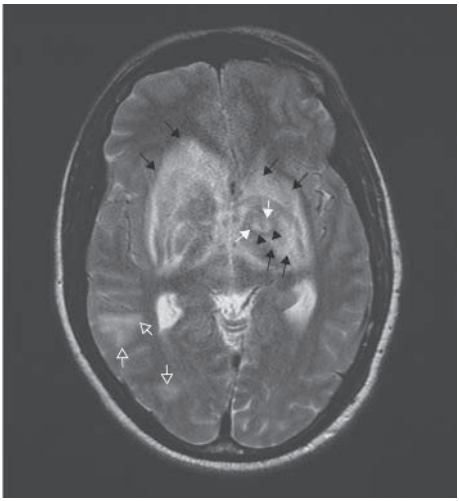

Figure 11.4 Cerebral toxoplasmosis (axial FLAIR MRI). Bilateral mass lesions (black arrows) with heterogeneous signal intensity in the deep gray nuclei. Target appearance is shown in the left anterior thalamus with a ring of hypointensity (black arrowheads) surrounding an area of hyperintensity (white arrows) and central hypointensity. Note also further lesions peripherally at the gray–white matter junction in the right temporo-occipital region (open white arrows).

Table 11.5 Treatment of opportunistic infections in HIV/AIDS

Disorder	Acute treatment	Maintenance	Comments
Toxoplasmosis	Pyrimethamine loading dose 100 mg/day PO, followed by 75 mg/day + folinic acid 15 mg/day + sulphadiazine 6–8 g/day IV/O	Pyrimethamine 25–50 mg/day + sulphadiazine 2–4 g/day + folinic acid 10 mg/day	If allergic to sulfa drugs use clindamycin 2.4–4.8 g/day. Maintenance 600 mg/day
Cryptococcal meningitis	Amphotericin B, 0.4–1.0 mg/kg/day IV ± flucytosine, 100 mg/kg/day PO	Fluconazole, 200 mg/day/PO	In mild cases fluconazole, 400 mg IV PO may be used

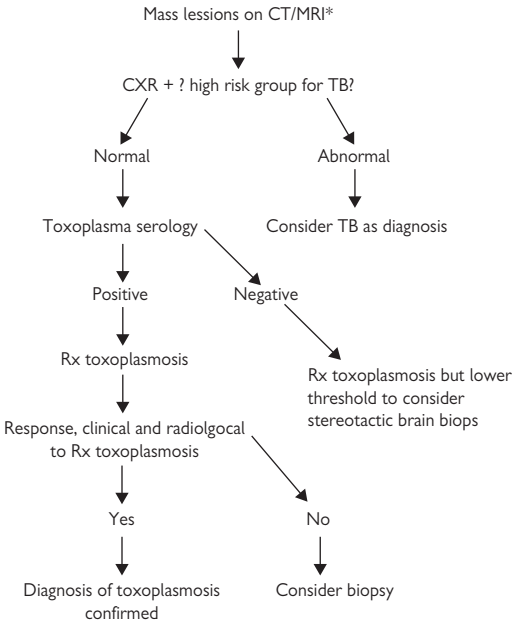

Figure 11.5 Algorithm for the management of mass lesions (CD4 count less than 200/mm3) as detected on CT/MRI (MRI is preferred as more sensitive). If increased ICP, treat with dexamethasone 4 mg q6hr. Once improved, gradually taper. Benefit may be due to decreased edema or response if lymphoma. At least 2 weeks may be necessary to assess for a response to anti-toxoplasmosis therapy. In some cases, providing there is no urgency, one may need to wait 1 month.

  - Serum cryptococcal antigen measurement may be a useful screening method in those with mild nonspecific symptoms
- Poor prognostic markers
  - Altered mental state
  - CSF OP >20 cmH_2O
  - CSF white cell count <10
  - Hyponatremia
  - Relapse episode

Treatment (See Table 11.5.)

- In mild cases where none of the poor prognostic markers are present, fluconazole is an alternative drug to amphotericin.

- May require repeated LPs for raised ICP. Consider insertion of a lumbar peritoneal shunt if frequent LPs required
- Acetazolamide may have an adjunctive role
- Acute phase Rx 4–6 weeks or until CSF culture negative

Progressive multifocal leukoencephalopathy (PML)

- Caused by reactivation of JC virus, a polyoma virus
- Subacute presentation with focal signs with no evidence of increased ICP
- Imaging
  - MRI shows nonenhancing focal white matter lesions with little or no mass effect on T2-weighted images
  - T1-weighted images show discrete low signal changes
- CSF: JC virus detected by PCR in 75%. Specificity 99%
- Blood serology unhelpful since 80% of the general population seropositive due to a childhood upper respiratory tract infection

Treatment

- HAART (highly active antiretroviral therapy) by improving immune function
- Cidofovir has anti-JC viral activity. Mixed reports when combined with HAART. Toxic side effects: nephrotoxicity, ocular hypotension
- Alpha interferon shown to have some benefit in one pre-HAART, open-labeled study

CMV infection

- May cause a meningoencephalitis
- Lumbar polyradiculopathy
- Retinitis
- Diagnosis: neutrophil pleocytosis in the CSF; CMV isolation in the CSF by PCR
- Treatment with ganciclovir or foscarnet

Fungal infections

Life cycle

- Fungi live as soil-dwelling saprophytes, producing reproductive spores.
- Fungal spores may adapt to higher temperature of human body and germinate.
- Pathogenic fungi can overwhelm or escape host defenses.
- Opportunistic fungi require impaired immune system for spores to germinate.

Pathogenesis

- Pathogenic—can infect healthy person though more common in the immunocompromised
  - Histoplasma
  - Blastomyces
  - Coccidiodes

- Paracoccidiodis
- Opportunistic—usually only seen in the immunocompromised patient
  - Aspergillosis—up to 95% mortality with CNS invasion
  - Candida
  - Cryptococcus: common in AIDS population—can be fatal within months
  - Rhizopus (extension from nasal sinuses and eye to brain; predisposition to infection in diabetic patients and leukemic patients)
  - Nocardia

Clinical features

- Meningitis or meningoencephalitis
- Abscess
- Arterial thrombosis

Diagnosis

- Can be difficult
- Clinical suspicion necessary
- Characteristic imaging
- Serum and CSF antigen and antibodies
- Demonstration of organism in tissue

Treatment

- Amphotericin B for most CNS fungal infections, may also consider flucytosine, -azoles, and caspofungin
- Specific treatments
  - Actinomycosis: penicillin or tetracycline
  - Nocardia: sulfa drugs

Parasitic infections

Parasitic infections have been uncommon in developed countries but are increasing in prevalence with immigration of persons from less-developed countries and with increased survival of immunocompromised patients.

- The two major categories of parasitic infections are represented by the helminths (worms) and protozoans (single-celled organisms).
  - Helminths—multi-celled organisms that elicit allergic reactions (eosinophilia); focal lesional involvement of the CNS; a diffuse meningitis may be present as well; seizures are common. Infections acquired by ingestion or injection of immature forms of life cycle. Animal hosts involved in life cycles
  - Tapeworms: *Taenia*, *Echinococcus*
  - Trematodes: *Schistosoma*, *Strongyloides*, *Paragonimus*
  - Nematode: *Angiostrongylus*, *Trichinella*, *Toxocara*
  - Protozoans—single-celled organisms; do not elicit allergic reactions or eosinophilia; diffuse involvement of the CNS with meningoencephalitis

- *Toxoplasma* (toxoplasmosis): prevalent in AIDS patient population
- *Plasmodium* (cerebral malaria): most common human parasitic disease; CNS involvement in 2%
- *Trypanosoma* (sleeping sickness and Chagas disease): African and South American diseases, respectively; arthropod-borne diseases
- Amebic infection: *Naegleria* (encountered in fresh water—invades CNS through olfactory epithelium—fatal) and *Acanthamoeba* (opportunistic—invades through lungs—fatal)

Prion diseases

Prions are abnormal proteins that cause a progressive spongiform encephalopathy and are transmissible. A prion induces a conformational change in normal proteins to an abnormal pathogenic form. The particular protein involved in disease in humans has been localized to the short arm of chromosome 20 (codon 129). A normal cellular isoform of protein (PRPc) exists; its function is unknown. The pathogenic form (PrPsc) occurs sporadically, as a genetic mutation, or is acquired (transmitted) from exposure to the abnormal protein through ingestion, transplantation of infected tissue, and injection by contaminated surgical instruments. All forms of prion disease are without treatment and uniformly fatal.

Kuru

- First human prion disease to be recognized
- Among natives of New Guinea who practice cannibalism
- Neuropathology—brain
  - Neuronal vacuolization and loss
  - Astrocytic vacuolization and proliferation
  - Amyloid plaques throughout, prominent in cerebellum
- Clinical features
  - Severe truncal and limb ataxia
  - Involuntary movements
  - Dementia
- Death within 4–24 months of symptoms

Creutzfeldt-Jacob disease

CJD is a human transmissible spongiform encephalopathy. Prion protein (PrP) gene contains a polymorphic locus at codon 129 encoding methionine or valine. Important in determining susceptibility to sporadic and acquired forms.

- Sporadic CJD, 85%–90% cases
- Familial forms, 10%–15% cases
  - Familial CJD
  - Gerstmann–Straussler–Scheinker
  - Fatal familial insomnia
- Iatrogenic CJD (human pituitary derivatives, dura mater, and corneal grafts), 1%
- Variant CJD: acquired by ingestion of contaminated meat

Sporadic Creutzfeldt-Jakob disease (sCJD)

- Rare disease (1:1,000,000) of middle-aged and older persons: mean onset seventh decade, range 15–94)
- Neuronal loss, astrocytosis, and vacuolization (giving spongiform appearance of brain on microscopic examination)
- Clinical features
  - Rapid dementia
  - Weakness and/or spasticity
  - Stimulus-sensitive myoclonus
  - Extrapyramidal signs
  - Seizures
  - Cerebellar dysfunction
  - Cortical blindness (rare)
  - Amyotrophy (rare)
- Diagnostic criteria. See Box 11.1
- Lab/Imaging/neurophysiology
  - CSF: 14–3-3 protein in 90% (not specific, but supportive); normal white cell count; moderately elevated protein
  - EEG: periodic triphasic complexes (60%)
  - MRI: T2/FLAIR/DWI hyperintensity in putamen, caudate, cortical ribbon and thalamus; cerebral atrophy (see Fig. 11.6)
  - PrP gene codon 129 polymorphism status
- Pathology: random misfolding in the prion protein (PrP) or somatic mutation in encoding gene causes the disease. Key pathological features in the brain
  - Spongiform changes
  - Neuronal loss
  - Astrocytosis
  - PrP deposition demonstrated by immunocytochemistry.
- Fatal within 1 year in 90% of cases

Box 11.1 Diagnosing sporadic CJD

Diagnostic criteria

- I Rapidly progressive dementia (if >2 years diagnosis doubtful)
- II Group of symptoms, including the following:
  - Myoclonus
  - Visual or cerebellar symptoms
  - Pyramidal or extrapyramidal features
  - Akinetic mutism
- III Typical EEG

Definite diagnosis

Neuropathology/immunochemistry confirmed

Probable diagnosis

Criterion I plus at least two from criterion II plus criterion III or "possible diagnosis" plus positive for protein 14–3-3.

Possible diagnosis

Criterion I plus at least two from criterion II and duration <2 years

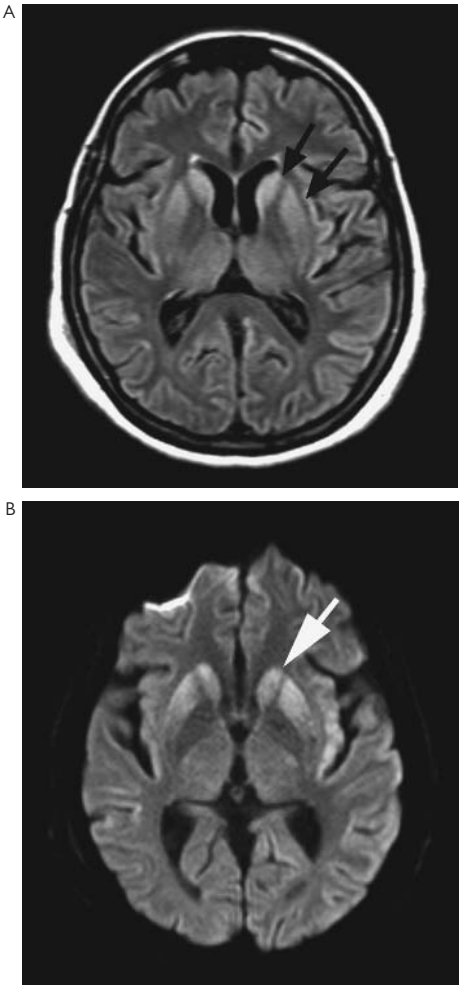

Figure 11.6 Sporadic Creutzfeldt–Jakob disease (sCJD). (A) FLAIR axial and (B) diffusion-weighted (DWI) MRI. Bilateral symmetric hyperintensity involving the striatal nuclei (black arrows). With less prominent involvement of the pulvinar and medial nuclei of the thalami bilaterally. (B) Note the more conspicuous signal change and increased sensitivity on DWI. .

Differential diagnosis
- AD
- Cerebral vasculopathy—inflammatory, lymphoma
- Chronic encephalitis—Hashimoto encephalitis, SSPE
- Paraneoplastic encephalitis
- Demyelinating disorders

Variant Creutzfeldt-Jakob disease (vCJD)

vCJD is the human form of bovine spongiform encephalopathy (BSE). Dietary transmission by ingestion of cow products is the most likely source.

Epidemiology: Patients affected: typically 14–50 years though older patients have been reported. All homozygous MM at codon 129.

Pathology: Florid amyloid plaques in cerebrum and cerebellum; spongiform change in caudate and putamen; accumulation of abnormal PrP demonstrated by immunocytochemistry. There is widespread accumulation of abnormal PrP in lymphoid tissue (tonsils and spleen).

Clinical features (early)
- Psychiatric symptoms
  - Depression
  - Withdrawal
  - Aggression and irritability
  - Anxiety, fear
  - Hallucinations and delusions
- Sensory symptoms (thalamic)
  - Limb pain
  - Paresthesias and dysesthesias
  - Numbness
  - Cold or burning sensations

Later features
- Ataxia
- Movement disorders—myoclonus, choreiform movements, dystonia
- Cognitive impairment

Progression is less rapid than for sCJD—mean duration 14 months.

Differential diagnosis
- Wilson disease (copper, ceruloplasmin levels, 24 hour urinary copper, and slit lamp exam for Kayser–Fleischer rings)
- AD
- Cerebral vasculitis
- Vitamin B_{12} deficiency
- Infective encephalitis
- Paraneoplastic syndrome

Investigations
- MRI: bilateral, symmetrical high signal in the posterior thalamus ("pulvinar sign"; see Fig. 11.6B)
- EEG: normal or nonspecifically abnormal. Triphasic complexes not seen

- CSF: normal WCC; protein mild–moderate elevation. 14–3-3 increased in 50%. Less sensitive than for sCJD
- PrP gene codon 129 status
- Tonsil biopsy may be considered but is not routine. A positive tonsillar biopsy does *not* make a diagnosis of "definite vCJD."
- Brain biopsy only if there is a possibility of a treatable disorder that cannot be diagnosed by other methods, e.g., vasculitis

Management

- Supportive and palliative
- vCJD is not transmissible by ordinary contact or body fluids, but invasive procedures require specific precautions.

Gerstmann-Straussler-Scheinker disease (GSS)

- Autosomal dominant familial prion disease
- Variable onset of symptoms (20s to 70s)
- Clinical course
  - Ataxia followed by dementia over 2 to 10 years
  - Brainstem involvement
  - Degeneration of spinocerebellar and corticospinal tracts
  - Widespread amyloid deposition
- Labs/imaging/neurophysiology
  - CSF: normal (no 14–3-3 protein)
  - MRI: generalized atrophy
  - EEG: diffuse slowing

Fatal familial insomnia (FFI)

- Autosomal dominant familial prion disease
- Wide range of onset of symptoms (18–61 years)
- Clinical symptoms
  - Progressive insomnia and dysautonomia
  - Pyramidal and cerebellar signs
  - Dementia
- Lab/imaging/neurophysiology
  - MRI usually normal
  - Labs usually normal
- On autopsy, neuronal loss and gliosis in thalamus with little or no spongiform findings. With protracted course, neuronal loss also seen on more widespread basis

Multiple sclerosis: introduction and clinical features

Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the CNS defined by episodes of demyelination disseminated in time and neuroanatomical location.

Epidemiology

- In the US, 250,000 individuals affected

- Prevalence 100/100,000 in United States
- Female:male ratio ~2:1; females with onset of disease 5 years earlier than males on average
- Rare before puberty and after the age of 60 years
- Peak incidence in 20s and 30s
- Incidence higher with increasing latitude
- Geographic and racial variation in prevalence worldwide

Pathogenesis

- Not fully elucidated, but thought to be an autoimmune inflammatory disorder with primary feature of T cells autoreactive to myelin in the CNS
  - Inflammation and blood–brain barrier disruption early in demyelinating plaque formation
  - TH1 activation
  - Myelin reactive T cells
- Multiple pathways for tissue damage
  - Primary axonal loss also occurs and is not clearly immune mediated
  - Several histologically discrete types of plaques described
- An association with class II alleles of the major histocompatibiliity complex (MHC) suggests genetic susceptibility triggered by an environmental factor, e.g., chronic infection with EBV or HHV6

Disease patterns

- Relapsing-remitting—subacute evolution of symptoms over days; symptoms reach a plateau and resolve completely or partially over days or weeks; no progression of symptoms between relapses
- Relapsing progressive—characterized by episodes of new symptoms, which may remit to some degree; however, there is slow progression of symptoms between relapses
- Primary progressive—accumulation of deficits without remission from onset of disease
- Secondary progressive—accumulation of deficits without remission after a period (up to 9–10 years) of relapsing-remitting MS

Clinical features

- Transverse myelitis
  - Weakness, sensory symptoms
  - Urinary urgency and retention
  - Flexor spasms
  - Spastic quadri- or paraparesis
  - Sensory level
- Brainstem
  - Ataxia
  - Diplopia
  - Dysarthria
  - Facial numbness
  - Internuclear ophthalmoplegia
  - Gaze palsy
  - Rubral tremor

- Cerebellum
  - Ataxia, dysarthria, nystagmus
- Optic neuritis: visual loss, painful eye movements, relative afferent pupillary defect (RAPD), impaired color vision (tested with Ishihara color plates), decreased acuity, disk edema and hyperemia acutely, optic atrophy in chronic state. See Box 11.2
- Cerebral hemispheres: (subcortical white matter)
  - Poor memory
  - Disinhibition (late)
  - Dementia (late)
- Cortical
  - Epilepsy (10%)
- Characteristic symptoms/signs
  - Lhermitte sign: neck flexion causes paresthesias or tingling down the spine due to a cervical cord plaque. Other causes: B_{12} deficiency, cervical spondylosis, or tumor
  - Uhtoff phenomenon: worsening of symptoms, e.g., vision, when body temperature is raised due to, e.g., exercise
  - Internuclear ophthalmoplegia. Other causes: vascular, Wernicke encephalopathy, pseudo-INO in MG

Course of disease

- Eighty-five percent present with relapsing/remitting disease (RRMS)
  - Average age of onset is 24–29 years
  - Females affected > males

Box 11.2 Optic neuritis and its association with MS

Optic neuritis—inflammatory demyelination of the optic nerve

- Presenting symptom in 30% of patients who developed MS within 5 years in Optic Neuritis Treatment Trial (ONTT)
- Fifty percent of MS patients will have optic neuritis at some time
- Thirty–five percent recurrence rate; recurrence associated with increased risk of developing MS

Prognosis with regard to developing MS

- ON (single episode) and normal brain MRI: <10% probability to progress to MS
- ON and three or more typical MRI lesions: >80% progress to MS

Treatment of ON

- There is no treatment that influences ultimate visual outcome.
- IV corticosteroids will hasten recovery of vision during a demyelinating episode and may delay onset of MS.
- Oral corticosteroids are ineffective in treatment of ON and may lead to worse visual outcome than with no treatment.
  - Institution of chronic immune-modifying therapy, e.g., interferons, in otherwise asymptomatic patients with ON and two or more brain lesions consistent with those seen in MS reduces rate of progression to clinically definite MS.

- After 10–15 years, 50%–60% enter the secondary progressive phase some with relapses (SPMS)
- Ten percent have primary progressive disease (PPMS) with gradual accumulation of disability
  - Average age of onset is 35–39 years
  - Males affected > females
- Disability accrued throughout disease course is measured by the Kurtzke Disability Status Scale (see Appendix, p. 452) and its extended scale (EDSS)

Multiple sclerosis: investigations and diagnosis

Investigations

MRI (see Figs. 11.7 and 11.8)

- T2W high signal changes seen in the corpus callosum, periventricular white matter, brainstem
- In patients >50 years, white matter lesions are less specific as they are found in normal individuals and those with cerebrovascular disease and migraine.

Evoked responses

- Visual evoked responses (VER): delay is the most sensitive method of demonstrating previous optic neuritis after clinical recovery or in subclinical disease
- Somatosensory evoked potentials (SSEP) and brainstem evoked potential (BSEP) less useful

CSF oligoclonal bands (OCB)

- Presence of OCB in the CSF not in the serum indicate inflammation confined to the CNS
- Positive in 95% of clinically definite MS
- May be present in other disorders such as paraneoplastic syndromes, vasculitis, autoimmune disorders, infections

Diagnosis of MS

See Box 11.3 for the McDonald criteria for diagnosis of MS.

- MS is a clinical diagnosis with a prerequisite of evidence of lesions disseminated in time and space and to the exclusion of mimics.
- It is not possible to diagnose MS after a single monophasic episode even if there are multiple lesions on MRI as there is no dissemination in time.
- After an isolated episode of demyelination, an abnormal brain MRI suggests that the likelihood of suffering a further attack and therefore of making a diagnosis of MS is 90% compared to 15% if the brain MRI is normal.

Differential diagnosis

ADEM. See p. 322.

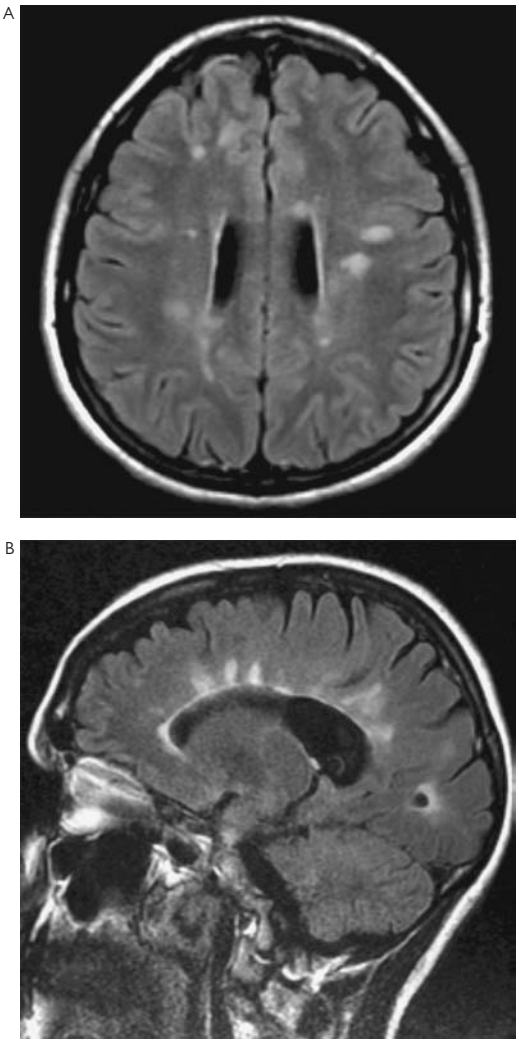

Figure 11.7 Multiple sclerosis MRI: axial (A) and sagittal (B) Flair-weighted images demonstrate numerous hyperintense white matter lesions with characteristic "Dawson's fingers" along the pericallosal white matter in patients with multiple sclerosis.

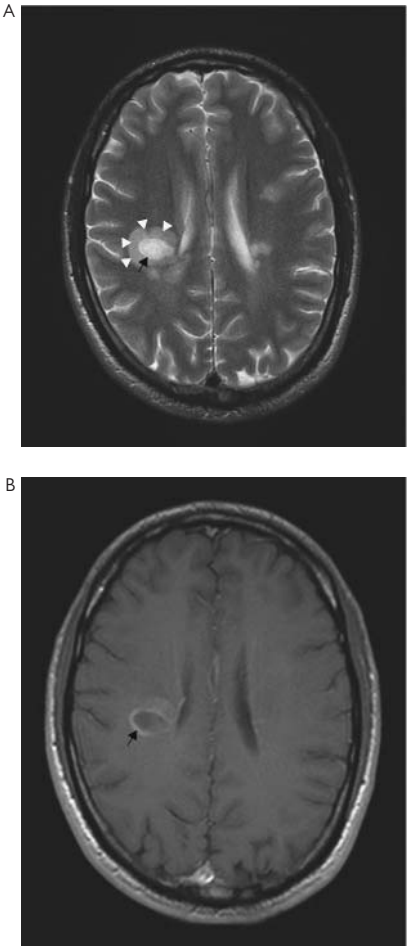

Figure 11.8 Acute presentation of MS. (A) Axial T2-weighted and (B) axial postcontrast enhanced MRI. Several rounded hyperintense lesions in the deep cerebral white matter. The largest in the right corona radiata ([A] black arrow) is surrounded by a halo of slightly less hyperintensity ([A] white arrowheads) and demonstrates an incomplete ring of enhancement ([B] black arrow).

Box 11.3 McDonald criteria for diagnosis of MS[1]

- Two or more episodes; objective clinical evidence of two or more lesions
- No additional tests required.

Two or more episodes; objective clinical evidence of one lesion

- Dissemination in space shown by MRI (nine or more T2 lesions or one Gd-enhancing lesion) or equivocal MRI (two or more lesions) + OCB in CSF or await further clinical episode at a different site.

One episode; objective clinical evidence or two or more lesions

- Dissemination in time shown by MRI or second clinical episode.

One episode; objective clinical evidence of one lesion

- Dissemination in space shown by MRI or equivocal MRI + OCB in CSF *and*
- Dissemination in time shown by MRI or second clinical episode

Insidious neurological progression suggestive of MS

- Positive OCB in CSF *and*
- Dissemination in space shown by MRI or abnormal VEP associated with equivocal MRI *and*
- Dissemination in time shown by MRI or continued progression for 1 year.

Note: MRI criterion for dissemination in time is that MRI of brain and/or cord after at least 3 months should show new disease activity with at least one Gd-enhancing lesion.

1 McDonald, WI, et al. (2001). Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol*: **50**:121–127.

Neurosarcoidosis. See p. 323

Neuromyelitis optica (Devic disease). See p. 321

Other mimics

- SLE
- Behçet disease
- Lyme disease
- Primary CNS vasculitis
- Leukodystrophies

Multiple sclerosis: management

Acute relapses

- Corticosteroids hasten recovery
  - IV methylprednisolone 500–1000 mg daily for 3–7 days with or without a short steroid taper
  - Oral methylprednisolone 500 mg–2 g daily for 3–5 days; caveat: not recommended if optic neuritis present—may increase recurrence rate

- Side effects (intravenous): flushing, psychiatric disturbance, insomnia, hyperglycemia, hypertension. Exclude infection prior to treatment (urinalysis). Rarely, aseptic bone necrosis reported

Disease-modifying treatments (DMT)

- Interferon beta is a natural cytokine with effects on the immune system.
  - Three injectable preparations are available: IFN beta-1b (Betaseron©); IFN beta-1a (Avonex©); IFN beta-1a (Rebif©)
  - Development of neutralizing antibodies may limit efficacy
  - Side effects include injection site reactions, flu-like symptoms, fatigue, and depression
- Glatiramer acetate (Copaxone) is a combination of amino acids.
  - Neutralizing antibodies detected in some studies—unclear significance
  - Side effects include injection site reactions, chest pain, flushing, dyspnea, and anxiety
- All drugs decrease frequency of relapse by one-third: i.e., from 3 to 2 relapses over 3 years.
- IFN beta reduces progression of disability compared to placebo. It is not clear if this is sustained.
- The effect of IFN beta in secondary progressive disease is unclear. May be effective in those with superimposed relapsing disease.
- IFN beta shows no effect in primary progressive disease.

In patients with aggressive disease unresponsive to IFN:

- Mitoxantrone. Limited by lifetime cumulative dose owing to cardiac toxicity
- Monoclonal antibodies natalizumab and alemtuzumab (Campath-1H) should be considered. Natalizumab (Tysabri) is in clinical use and is highly effective but has induced progressive multifocal leukoencephalopahthy in 5 patients thus far (of about 14,000 treated). Alemtuzumab, rituximab, and other monoclonal antibodies are under study.

Other DMT options

- Immunosuppressive therapy: cyclophosphamide (pulsed or daily), azathioprine, mycophenolate, or MTX for rapidly progressive or chronically progressing disability
- Plasma exchange for rapidly progressing disability
- IVIG reduces relapse rate; unclear if disease progression slowed
- Stem cell transplantation and total lymphoid irradiation considered in severe progressive forms of disease

Symptomatic treatment

Spasticity

- Treat any infections, constipation, pain
- Physiotherapy essential
- Baclofen starting 5 mg/day increased to 40 mg q8hr. Limited by side effects of sedation, muscle weakness
- Tizanidine starting 2 mg/day increased to 8 mg q8hr. LFTs need monitoring

- Dantrolene starting 25 mg/day increased to 100 mg q8hr. Monitor LFTs
- Gabapentin starting at 100 mg increased to 800 mg q8hr helps tonic spasms or phasic spasticity
- Focal spasticity, e.g., adductor spasm, use botulinum toxin
- In severe lower limb spasticity resistant to therapy, intrathecal baclofen via a pump

Bladder dysfunction

There are three aspects of neurogenic bladder dysfunction:

- Detrusor hyperreflexia characterized by reduced capacity, urgency, frequency, and incontinence
- Detrusor/sphincter dyssynergia associated with urgency, delayed emptying, retention
- Bladder hyporeflexia characterized by incomplete emptying and increased residual urine. All three may be present simultaneously.

Symptomatic treatment includes the following:

- Even distribution of fluid intake (2 L/day)
- Pelvic floor exercises help urgency and incontinence.
- Measure residual urine volume by catheter or bladder US. If >100 mL, consider intermittent self-catheterization. May be limited by disability
- Detrusor hyperreflexia treated with
  - Oxybutynin 2.5 mg bid–5 mg bid
  - Oxybutynin XL 5 mg daily
  - Tolterodine 2–4 mg/day
  - Tolterodine XL 4 mg daily
- Nocturia managed by intranasal desmopressin 10–20 μg. Side effect hyponatremia

Fatigue

Fatigue is common and worsened by heat.

- Exclude other causes, e.g., decreased Hb, increased T4
- Fatigue management classes with aerobic training
- Screen for depression and treat
- Amantadine, 100–200 mg daily
- Modafinil, 100–200 mg daily

Neuromyelitis optica (Devic disease)

Neuromyelitis optica is felt to be closely related to multiple sclerosis, but specific diagnostic criteria set it apart as a separate entity. Key features are as follows:

- Optic neuritis and myelitis occurring together or in succession
- Spinal cord lesion three or more segments in length or NMO-IgG antibody positivity

Other CNS involvement is allowable as long as the above criteria are met.

Features

- Onset of disease can be fulminant with severe deficits—element of necrosis in addition to demyelination can be demonstrated

- Prognosis for recovery of vision and spinal cord function is guarded.
- Primary progressive or relapsing-remitting

Treatment

Treatment should be aggressive given the severity of disease. Consideration should be given to long-term immunosuppression in relapsing-remitting forms.

- Plasma exchange (seven exchanges on alternate days in acute phase), plus IV methylprednisolone 1 g on alternate days x5)—alternating plasma exchange and IV methylprednisolone treatments
- Long-term immunosuppression with steroid-sparing agents such as azathioprine combined with oral prednisone has been used to decrease relapse rates; observational studies suggest that mitoxantrone, IVIG, or rituximab may be effective in this regard as well.

Acute disseminated encephalomyelitis (ADEM)

ADEM is also known as postinfectious encephalomyelitis and postvaccinal myelitis as it occurs during or following viral or bacterial infection or following vaccination.

Pathogenesis

- An autoimmune reaction targeting central myelin
- Can be triggered by many viruses and vaccines
- No viral particles have been isolated from areas of demyelination
- Any area of the brain or spinal cord can be affected
- Numerous demyelinated plaques with sharp edges primarily in white matter
- Perivenular lymphocytic and mononuclear cell infiltration

Clinical features

- Meningeal involvement is common, leading to meningismus and headache
- Irritability, stupor, or coma
- Any (and many) portions of the brain parenchyma may be affected, leading to focal symptoms and signs
  - Aphasia
  - Hemiplegia
  - Bilateral optic neuritis
  - Cranial nerve palsies
  - Ataxia
- Spinal cord involvement is common: acute transverse myelitis
  - Often at thoracic levels—affecting motor and sensory tracts
  - Back pain
  - Ascending sensory loss
  - Paraparesis
  - Bowel and bladder dysfunction

Diagnosis

- Clinical history—neurologic signs occurring within 1 month of viral infection (particularly exanthematous), upper respiratory infection, or vaccination
- Supportive imaging of multiple, uniformly enhancing, large demyelinating lesions of brain or spinal cord; gray matter may be involved
- LP: increased protein, normal glucose, mildly increased MBP, mildly increased WBC (lymphocytic predominance); OCB positive in 30% and may disappear
- EEG: nonspecific generalized slowing; possible focal slowing related to lesions
- "No other cause found"—differential includes all other inflammatory demyelinating disorders

Treatment

ADEM is monophasic and self-limiting most commonly, but it may be recurrent. Treatment may be instituted to reduce or limit neurologic deficits.

- ACTH or corticosteroids
- IVIG
- Plasma exchange

Prognosis

- Related to preceding infection and severity, location, and extent of lesions
- Mortality rate up to 30% in patients with severe cerebral involvement
- In survivors, 90% with complete recovery (except after ADEM triggered by measles where deficits remain in up to 50% of patients

Acute hemorrhagic leukoencephalitis (AHL)

AHL represents a hyperacute and more severe form of ADEM. Lesions often are large, with hemorrhage, and exhibit mass effect. Prognosis is poorest for neurologic recovery in this form.

Neurosarcoidosis

Sarcoidosis is a granulomatous disease of unknown etiology that may affect any organ system. Greater than 90% of cases have pulmonary involvement. A pathognomonic feature of sarcoidosis is the noncaseating granuloma containing multinucleated giant cells and epithelioid cells.

Epidemiology

- Worldwide occurrence with prevalence of 3–50 (average 10–20) per 100,000
- Geographic and racial variation in prevalence worldwide
- In United States, highest prevalence in African Americans (2.4% lifetime risk vs. 0.85% in Caucasians)

Pathogenesis

- An immune reaction—T cell response—to unknown antigen(s). No infectious cause identified
- Susceptibility to and severity of disease associated with polymorphisms of the MHC

Clinical features

- Sarcoidosis—common systemic signs and symptoms
  - Fatigue, fever, anorexia
  - Dyspnea, cough
  - Rash—erythema nodosum
  - Arthralgias
  - Abnormal chest X-ray with hilar adenopathy

Lofgren syndrome

Hilar adenopathy, erythema nodosum, migratory polyarthralgias, and fever; female predominance.

Neurological involvement in sarcoidosis is present in 5% of all cases. Sarcoid granulomas can occur anywhere in the CNS or PNS, but they have a predilection for occurrence in cranial nerves and at the base of the brain.

- Sarcoidosis—neurologic involvement
  - Cranial neuropathy—present in >50% of cases of neurosarcoidosis: (most frequently cranial nerve VII)
- Parenchymal granulomas—focal or widely dispersed
  - Seizures
  - Cognitive changes
  - Infarction (rare)
  - Neuroendocrine function affected (predilection for hypothalamus)
  - Meningeal involvement
  - Aseptic meningitis
  - Hydrocephalus
  - Peripheral neuropathy—single or multiple mononeuropathies or polyneuropathy
  - Myopathy—palpable nodules or diffuse infiltration—focal or diffuse weakness

Heerfordt syndrome (uveoparotid fever)

Cranial nerve 7 palsy, uveitis, parotitis

Diagnosis

- Definitive diagnosis by tissue biopsy
- Supportive labs and imaging (if normal, diagnosis is not excluded)
  - Labs: serum calcium, ACE, sodium, endocrinologic studies
  - LP: CSF ACE, elevated protein, low glucose, elevated IgG index, white blood cells in CSF (lymphocytic predominance and with elevated CD4:CD8 ratio)
  - Chest X-rays, CT: hilar adenopathy, fibronodular disease
  - MRI (neuraxis): contrast enhancing nodules, meningeal and occasionally vascular enhancement (see Fig. 11.9)
  - Further testing and biopsy determined in individual cases by organ system involved

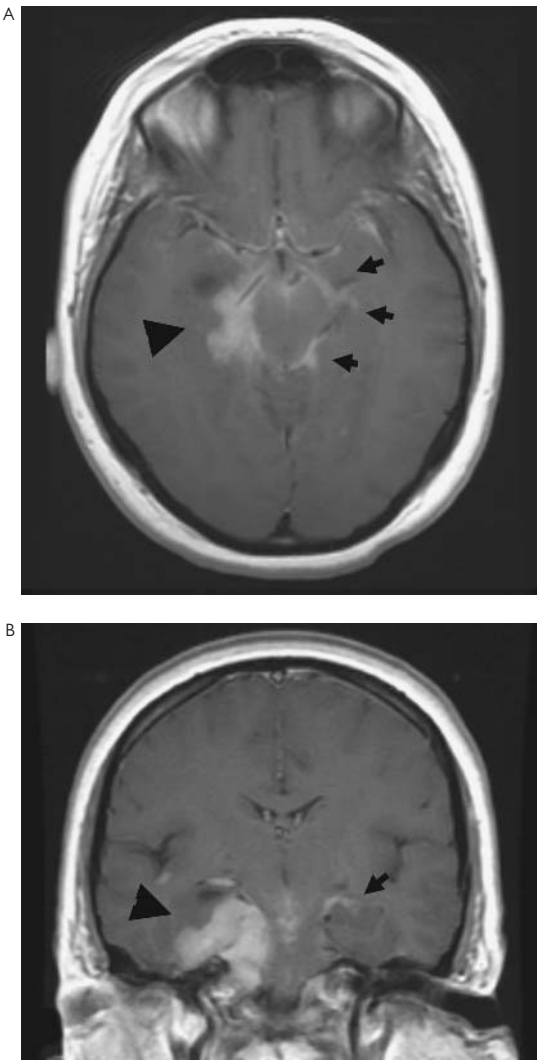

Figure 11.9 Neurosarcoidosis MRI: Axial (A) and coronal (B) T1-weighted postcontrast images demonstrate extensive bulky extraaxial enhancement throughout the skull base in a patient with known neurosarcoidosis.

Treatment

- None—with mild and/improving symptoms—disease is monophasic and spontaneously remitting in 67% of neurosarcoidosis
- Corticosteroids: 0.5–1.5 mg/kg/day orally (IV methylprednisolone at 20 mg/kg/day x 3 days may precede oral treatment with severe disease or rapid neurological deterioration). Taper according to severity of disease and response to treatment
- Steroid-sparing immunosuppressive medications for patients intolerant to steroids and/or with severe disease
- Azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, cyclosporine, chlorambucil, cladribine, infliximab, hydroxychloroquine, pentoxifylline, and thalidomide have all been used with some degree of success

Chapter 12

Neoplastic and paraneoplastic disorders

Stephen E. Sullivan, MD
Diana Gomez-Hassan, MD, PhD

Classification of intracranial tumors *328*
General management of intracranial tumors *331*
Management of specific tumor types *332*
Paraneoplastic syndromes *342*

Classification of intracranial tumors

Epidemiology

Intracranial tumors are the sixth most common neoplasm in adults and the most common solid tumors in children. Incidence of all primary brain tumors is 14–21/100,000/year.

Types of intracranial tumors

Primary brain tumors

- Pilocytic astrocytoma, grade I
- Astrocytoma, grade II
- Anaplastic astrocytoma, grade III
- Glioblastoma multiforme, grade IV (see Fig. 12.1)
- Oligodendroglioma
- Ependymoma
- Choroid plexus papilloma
- Neuronal tumors or mixed tumors (e.g., ganglioglioma)
- Embryonal tumors (medulloblastoma, PNET)
- Pineal parenchymal tumors

Other intracranial tumors

- Metastatic tumors (breast and lung most common)
- Meningeal tumors (meningioma)
- Vascular tumors (hemangioblastomas)
- Pituitary adenomas
- Germ cell tumors (germinoma, teratoma)
- Primary CNS lymphoma
- Nerve sheath tumors (vestibular schwannoma)
- Developmental tumors (epidermoid, craniopharyngioma, colloid cyst)
- Chondroid matrix tumors (chondrosarcoma, chordoma)

Etiology

- Most are sporadic.
- Cranial irradiation increases risk of meningioma.
- Von Hippel-Lindau syndrome is associated with hemangioblastoma.
- Neurofibromatosis I is associated with neurofibromas and optic nerve gliomas.
- Neurofibromatosis II is associated with vestibular schwannoma and meningioma.
- Tuberous sclerosis is associated with giant cell astrocytoma.

Clinical features

Symptoms from increased intracranial pressure

- Local mass effect
- Obstruction of CSF outflow (more common with posterior fossa lesions)

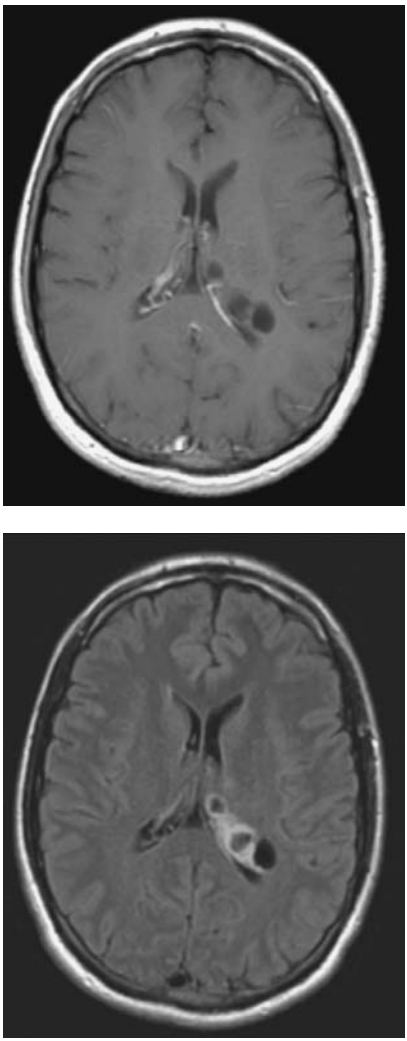

Figure 12.1 Low-grade glioma (MRI, [A], T1 with contrast, [B], FLAIR). Low-grade cystic astrocytoma compressing the left ventricular trigone demonstrating lack of pathologic contrast enhancement (A) and high FLAIR signal (B).

Other symptoms
- Headache (often worse in morning)
- Nausea/vomiting
- Ataxia
- Mental status changes
- Papilledema
- Diplopia (CNVI palsy due to increased intracranial pressure)

Progressive neurological deficits
- Supratentorial lesions present with cortical deficits
  - Hemiparesis
  - Hemibody neglect
  - Visual field deficit
  - Aphasia
  - Cognitive or behavioral changes (frontal lesions)
- Posterior fossa lesions
  - Appendicular and/or gait ataxia
  - Cranial nerve palsies
  - Diplopia
  - Hydrocephalus
- New onset seizure
  - Should prompt an investigation for neoplasm
  - Seizures are presenting symptom in 25% of tumors

Imaging features
- MRI +/− gadolinium most sensitive for tumor evaluation
  - Special high-resolution protocols necessary for some tumor evaluations (e.g., pituitary protocol, CN VIII protocol for vestibular schwannoma)
- CT a useful adjunct
  - Calcification (e.g., oligodendroglioma)
  - Calvarium remodeling (slowly growing neoplasms)
  - Skull base involvement (meningioma, chondrosarcoma)
- Cerebral angiogram
  - Useful for determination of tumor vascularity
  - Some tumor resections are preceded by endovascular embolization to decrease blood loss.

Other investigations
For metastatic workup
- Complete history and physical, including breast, GU, and rectal examinations
- Chest X-ray
- Chest/abdomen/pelvic CT
- Mammogram
- Bone scan
- PET scan
- Lumbar puncture for cytology when meningeal spread suspected (contraindicated for abscess or mass lesion)

For specific tumor types
- Ophthalmologic examination for CNS lymphoma to detect vitreous involvement
- Serum and CSF alpha feto protein, beta HCG and CEA for pineal region tumors (germ cell tumors)
- Total spine MRI for dropped metastases (ependymoma, medulloblastoma)

Differential diagnosis

Infection
- Abscess, encephalitis may mimic high-grade glioma
- Parasite
  - Cysticercosis, hydatid cyst

Vascular
- Cavernoma
- Arteriovenous malformation (AVM)
- Aneurysm

Inflammatory
- Acute MS plaque

General management of intracranial tumors

Management of tumors requires consideration of the following:
- Need for tissue diagnosis
- Location of lesion and possible postoperative deficits
- Likelihood that aggressive resection will or will not prolong survival
- Adjunctive therapies for specific tumor types (radiation, chemotherapy)
- Patient age and medical comorbidities
- Quality of life

Preoperative management

- Corticosteroids reduce vasogenic edema, useful in symptomatic patients
- Anticonvulsants are not routinely recommended in seizure-free patients
- Frequent neurological checks
- Maintain serum Na in normal range
- Avoid hypotonic IV fluids
- Elevate head of bed more than 30 degrees

Neurosurgical procedures

Stereotactic biopsy: Precise placement of a biopsy needle into a brain lesion to obtain a tissue diagnosis. Either frame-based or frameless using neuronavigation. Two percent risk of symptomatic hemorrhage.

Ommaya reservoir: Subcutaneous access device under scalp connected to a ventricular catheter, used to facilitate intrathecal chemotherapy (Rickham reservoir is a common alternative).

Neuronavigation: (e.g., Stealth, Brainlab) Computer-based device that allows the surgeon to register the patient's head and brain to preoperative imaging to allow precise localization during surgery.

Craniotomy: A bone flap is removed to allow increased visualization and room for tumor resection.

Management of specific tumor types

Astrocytoma

- Grade I (Pilocytic astrocytoma): may be cured surgically, excellent prognosis (Fig. 12.2)
- Grade II (low-grade astrocytoma): mean survival 5 years
  - Radiotherapy and aggressive resection may confer a survival advantage if safe to do so
  - May progress to glioblastoma (Fig. 12.1)
- Grade III (anaplastic astrocytoma): mean survival 2–3 years
  - Treated similar to GBM
- Grade IV (glioblastoma, GBM): mean survival 12 months
  - Treated with fractionated radiotherapy and concurrent temozolomide, an oral chemotherapeutic agent
  - Aggressive resection may confer a survival advantage

Meningioma

- WHO grade I: benign meningioma
  - Make up 85% of meningiomas
  - May have hormonal receptors (octreotide, progesterone)
- WHO grade II and III: anaplastic and malignant meningioma
  - High recurrence rate
  - Often treated with resection and radiotherapy
  - May be fatal

Indication for surgical management

- Radiographic growth
- Symptomatic mass effect or cranial neuropathies
- Most can be followed radiographically without resection

Surgical management

- Complete tumor resection requires removal of all involved dura and bone (hyperostosis).
- Subtotal resection has a high recurrence rate.
- Parasagittal tumors may involve the superior sagittal sinus.
- Skull base tumors (e.g., clivus, cavernous sinus) may be treated with subtotal resection and radiotherapy.
- Radiotherapy (conventional or stereotactic) is effective in controlling growth in up to 80% of tumors.

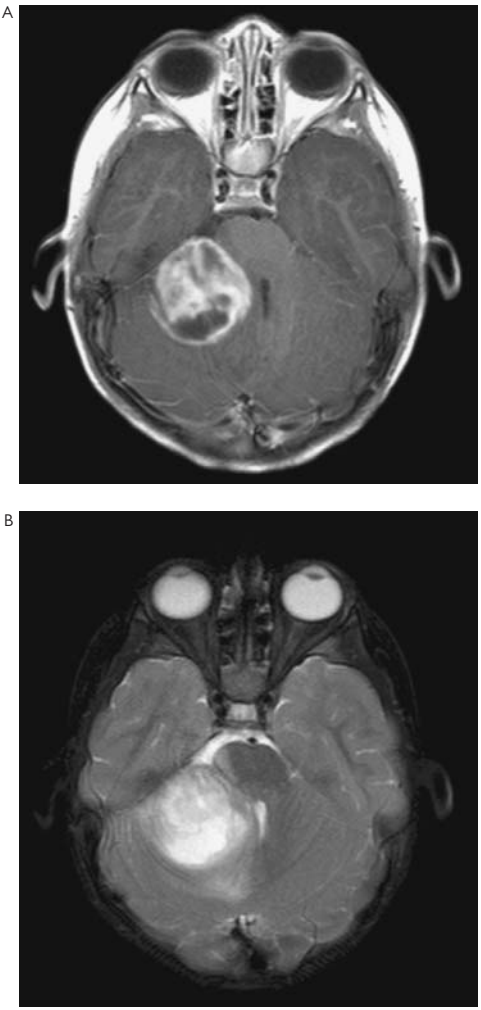

Figure 12.2 MRI (T1 with contrast, T2 weighted) of large right cerebellar hemispheric pilocytic astrocytoma centered in the right cerebellar peduncle and demonstrating pathologic contrast enhancement. This neoplasm is seen in children and young adults. (A) T1 weighted brain MRI with contrast. (B) T2 weighted sequence.

Primary CNS lymphoma

Extra nodal B cell lymphoma distinct from systemic lymphoma

Etiology

- Sporadic (age >55 years)
- Immunosuppressed
  - HIV
  - Transplant recipients

Clinical features

- Brain
  - Encephalopathy
  - Focal neurological deficit
  - Seizures
- Leptomeninges
  - Cranial nerve deficits
  - Polyradiculitis
  - Hydrocephalus
- Ocular
  - Vitreous hemorrhage
  - Uveitis

Diagnostic tests

- CT: iso- to hyperintense periventricular lesions
- MRI: periventricular enhancing lesions, dural enhancement if CSF involved
- LP: pleocytosis, flow cytometry may demonstrate monoclonal B cell population, frequently nondiagnostic
- Slit lamp exam: mandatory in all patients to rule out vitreous involvement (a common site for relapse)
- Stereotactic brain biopsy: most common diagnostic test, corticosteroids given preoperatively may decrease diagnostic yield by shrinking tumor

Treatment

- Avoid corticosteroids if possible
- Intravenous methotrexate, mean survival 4 years
- Intrathecal methotrexate for leptomeningeal involvement
- Radiotherapy

Cerebral metastasis

Etiology

- Most common intracranial tumor
- Hematogenous spread from systemic carcinoma (most commonly lung, breast, renal)

Clinical features

- Seizures
- Focal deficits

- Diffuse mass effect (encephalopathy, 6th nerve palsy)
- Multiple cranial neuropathies (carcinomatous meningitis)
- Acute hemorrhage (renal cell carcinoma, melanoma)

Imaging features

- Ring or solid contrast enhancement (Fig. 12.3)
- Often at the corticomedullary junction
- Single or multiple
- Intraparenchymal mass with history of carcinoma = 90% chance of metastasis

Treatment

- Corticosteroids if symptomatic mass effect
- If atypical presentation for metastasis, a tissue diagnosis should be obtained via craniotomy or stereotactic biopsy
- Surgical excision of 1–3 metastasis with whole-brain radiation confers greatest survival (9–12 months)
- Stereotactic radiosurgery is a reasonable alternative to open resection.
- Whole-brain radiotherapy alone is useful for patients with multiple metastasis.

Pituitary tumors

Classification

- Microadenoma: <1 cm
- Macroadenoma: >1 cm
- Nonsecreting adenomas
- Secreting adenomas
  - Prolactinomas
  - GH-secreting adenomas (acromegaly)
  - ACTH-secreting tumors (Cushing syndrome)

Nonpituitary origin sellar and suprasellar masses

- Craniopharyngioma
- Rathke pouch
- Germ cell tumor
- Histiocytosis X
- Sarcoidosis

Clinical features

- Hypopituitarism seen in nonsecreting macroadenomas
- Bitemporal hemianopsia: macroadenoma affecting central optic chiasm
- Galactorrhea, dysmenorrhea, infertility: prolactinoma
- Hypercortisolism, central obesity, stria, moon facies: Cushing disease
- Facial coarsening, cardiomyopathy, increase ring and shoe size: acromegaly
- Pituitary apoplexy: acute headache, ophthalmoparesis and visual loss due to adenoma infarction or hemorrhage

Diagnostic testing

- MRI pituitary protocol: normal pituitary tissue more enhancing than adenoma (Fig. 12.4)

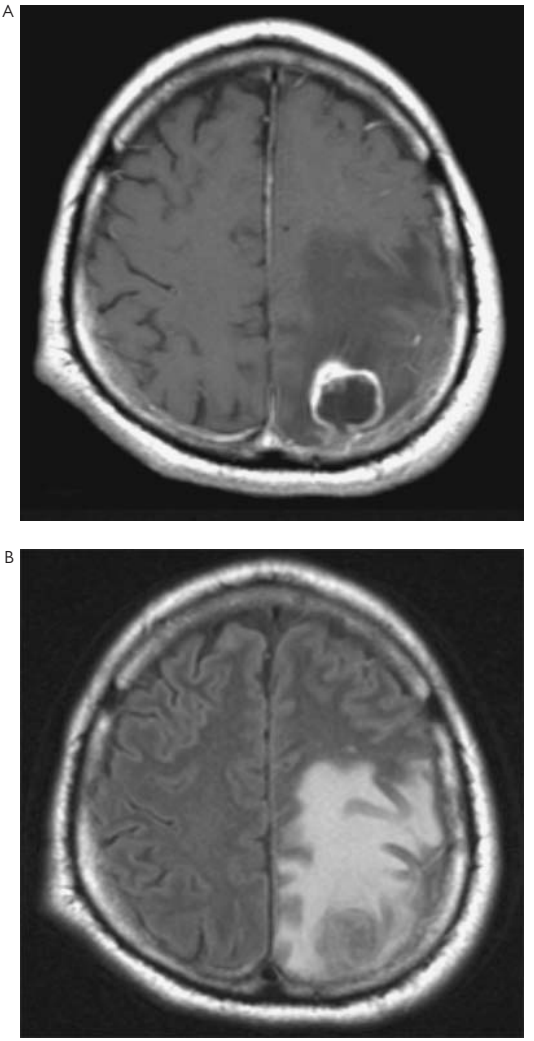

Figure 12.3 MRI of metastasis (T1 with contrast [A], FLAIR [B]). Left parietal lung carcinoma metastasis is seen demonstrating peripheral pathologic contrast enhancement (A) and diffuse high FLAIR signal throughout the surrounding cerebral white matter (B) consistent with tumor-associated edema.

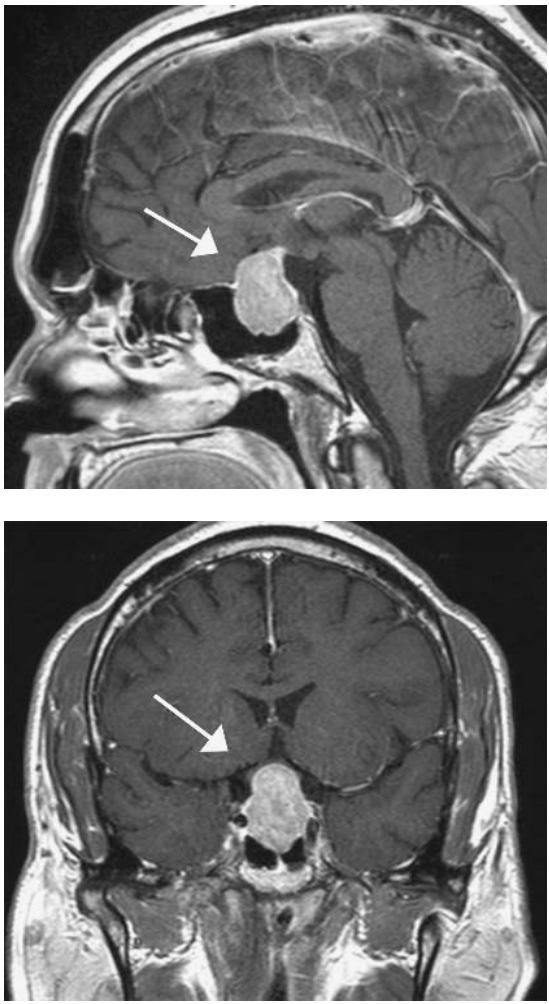

Figure 12.4 Pituitary adenoma (MRI, sagittal T1 with contrast [A] and coronal T1 with contrast [B]). Nonsecreting pituitary macroadenoma (white arrow) is seen as a bulky enhancing mass in the sella and suprasellar cistern presenting with bitemporal hemianopia. Note that the optic chiasm is displaced upward over the top of the tumor (B).

- Ophthalmologic referral for visual field testing to ensure normal chiasm
- Petrosal venous sinus sampling: hormonal testing directly from the petrosal sinus can help localize a small adenoma not seen on MRI (esp. Cushing microadenoma)
- Hormal testing necessary for all pituitary tumor patients
  - TSH, Free T4, LH, FSH, GH, PRL, am cortisol. Somatomedin C (for acromegaly)
  - Note mild elevations of prolactin may be seen in macroadenomas other than prolactinomas (stalk effect)

Treatment

- Hormone replacement: as needed based on endocrinologic workup
- Surveillance MRI: for asymptomatic nonsecretory adenomas, no treatment necessary
- Prolactinomas
  - For symptomatic prolactinomas, initial treatment is medical, not surgical.
  - Bromocriptine or other dopamine agonist will reduce and/or control most prolactinomas.
  - Surgery is used only for prolactinomas not responsive to medical therapy or in the case of progressive visual deficit.
- ACTH-secreting tumors, Cushing disease
  - Transphenoidal surgery is first-line treatment
  - Often difficult to locate microadenoma
  - Recurrences treated with repeat surgery or radiation
  - Adrenelectomy reserved for cases that do not respond to pituitary exploration
- GH-secreting tumors, acromegaly
  - Transphenoidal surgery is first-line treatment
  - High incidence of cardiac dysfunction
  - High recurrence rate
  - Octreotide lowers GH production

Acoustic neuroma (vestibular schwannoma)

Etiology

- Benign tumor arising from vestibular nerve schwann cell
- Unilateral tumors usually sporadic
- Bilateral tumors associated with neurofibromatosis II

Clinical features

- Sensorineural hearing loss
- Tinnitus
- Vertigo
- Facial weakness
- Dyscoordination
- Hydrocephalus (large tumors only)

Diagnostic investigation
- Audiometry
- Thin cut temporal bone CT: expansion of internal auditory canal (IAC), anatomy of cochlea and labyrinth important intraoperatively
- MRI: thin cuts through cerebellopontine angle

Other CPA masses
- Meningioma, dural tail, does not widen IAC
- Epidermoid, restricts diffusion
- Trigeminal schwannoma
- Chondrosarcoma (Fig. 12.5)
- Glomus jugulare
- Metastasis

Treatment
- Surgical excision is curative.
- Stereotactic radiosurgery and fractionated radiotherapy can control tumor growth.
- Morbidities include facial nerve palsy, hearing loss, and CSF leak through mastoid air cells.
- Retrosigmoid approach is useful for large tumors or for hearing preservation.
- Translabyrinthine approach avoids cerebellar retraction in patients with no serviceable hearing.
- Middle fossa approach is used for intracanilicular tumors.

Spinal tumors

Classified by location:

Intradural intramedullary tumors
- Tumors that arise in the spinal cord parenchyma
- Glioma
- Ependymoma
- Hemangioblastoma
- Metastatic tumors
- Syringomyelia (may or may not be due to tumor)

Intradural extramedullary tumors
- Tumors arising outside the spinal cord but within the dura
- Meningioma
- Schwannoma, neurofibromas (nerve sheath tumors)(Fig. 12.6)
- Myxopapillary ependymoma
- Drop mets from intracranial ependymoma, medulloblastoma, germ cell tumor
- Epidermoid

Intraosseus tumors
- Those arising within the bony spine
- Osteoma/osteoblastoma

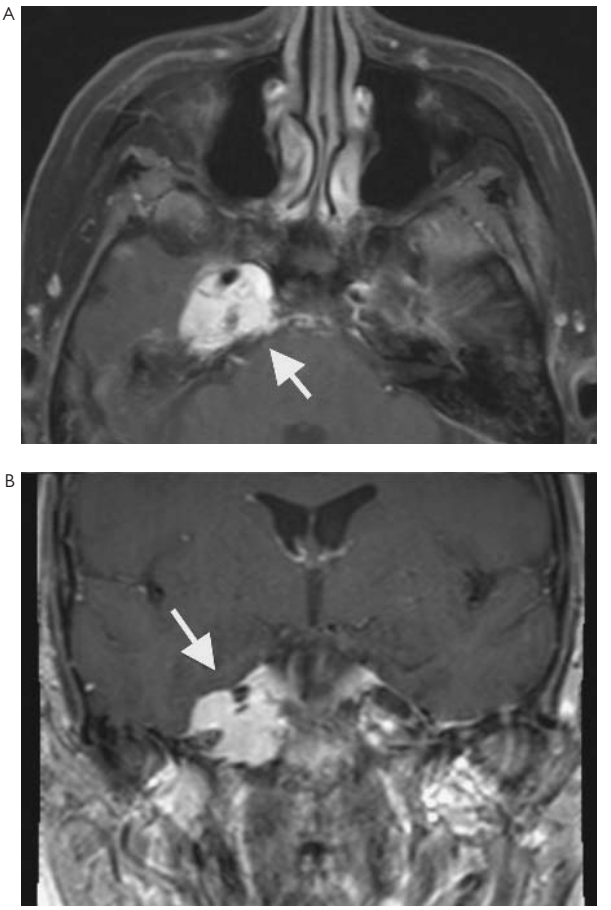

Figure 12.5 Chondrosarcoma (MRI, axial T1 with contrast [A] and coronal T1 with contrast [B]). Chondrosarcoma of the right petroclival synchondrosis (white arrows) presenting with 6th nerve palsy.

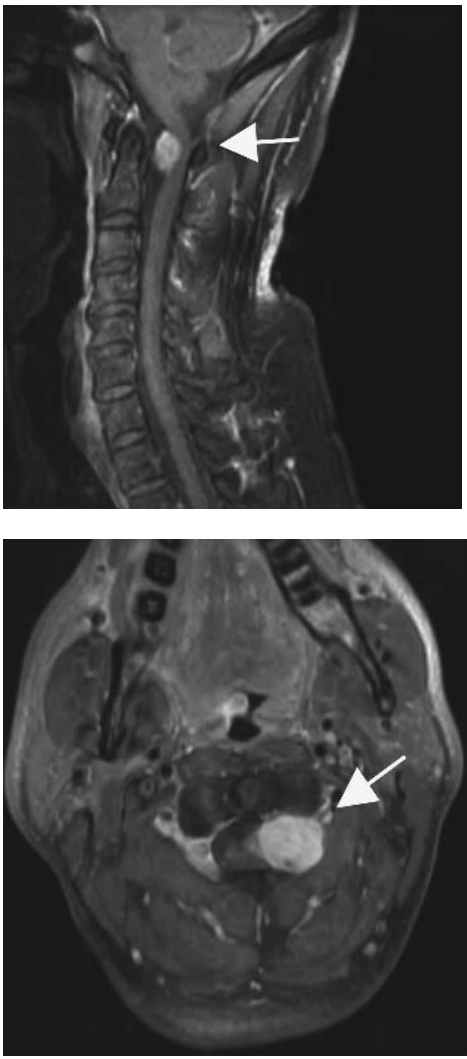

Figure 12.6 MRI of cervical schwannoma (cervical MRI, T1 sagittal with contrast [A], T1 axial with contrast [B]). C1,2 schwannoma (white arrows) with both intra- and extradural components causing spinal cord compression.

- Giant cell tumor
- Metastasis (most common)
- Chordoma (sacrum or cervical levels 1,2)
- Paget disease and fibrous dysplasia may mimic tumors.

Treatment

- Symptomatic lesions are generally surgically excised via laminectomy if safe.
- Intramedullary tumors may be biopsied only.
- Intramedullary pilocytic astrocytomas and ependymomos may be safely resected.
- Radiotherapy for residual disease

Paraneoplastic syndromes

Introduction

- Defined as neurological effects associated with a malignancy that cannot be explained by cancer invasion, metastasis, or complications of cancer treatment
- Paraneoplastic syndromes often present before cancer diagnosis.
- May be associated with early-stage cancer
- Antibody mediators have been identified
- Some antibodies are associated with more than one clinical syndrome (see Table 12.1).

Paraneoplastic syndromes: central nervous system

Subacute cerebellar degeneration

- Gait unsteadiness, diplopia, dysphagia
- May be preceded by a viral-like prodrome
- Often rapid onset
- Brain MRI may reveal cerebellar atrophy or folia enhancement
- Extensive loss of Purkinje cells and inflammation of deep cerebellar nuclei pathologically

Associated cancers

- Small-cell lung
- Ovarian
- Breast
- Hodgkin lymphoma

Opsoclonus myoclonus

- "Dancing eyes, dancing feet" syndrome
- Involuntary arrhythmic multidirectional saccades with horizontal, vertical, and torsional components
- Myclonic jerking of limbs and trunk
- Ataxia, tremor, encephalopathy
- Results from disinhibition of the cerebellar fastigial nucleus
- Strongly associated with neuroblastoma in children
- Adult tumors include small-cell lung cancer, breast and ovary
- Antibody testing is negative in most patients.

Table 12.1 Paraneoplastic disorders, associated antibodies, and cancer types

Syndrome	Paraneoplastic antibody	Associated cancer
Lambert–Eaton myasthenic syndrome (LEMS)	VGCC	SCLC
Subacute cerebellar degeneration	Anti-Hu	SCLC
	Anti-PCA-2	SCLC
	Anti-Yo	Ovary, breast
	Anti-Ta/Ma2	Testis
	Anti-Ri	Breast
	Anti-Tr	Hodgkin's lymphoma
Opsoclonus/myoclonus (children)	Anti-Hu	Neuroblastoma
Opsoclonus/myoclonus (adult)	Anti-Ri	Breast
	Anti-Hu	SCLC
	Anti-Ma	Various
	Anti-ta/Ma2	Testis
Subacute sensory neuropathy/neuronopathy	Anti-Hu	SCLC
	Anti-amphiphysin	SCLC
	ANNA-3	SCLC
	Anti CRMP5/CV2	SCLC, thymoma
Limbic encephalitis	Anti-Hu	SCLC
	Anti-Ta/ma2	Testis
	ANNA 3	SCLC
	Anti-CRMP5/CV2	SCLC, thymoma
Retinopathy	Anti-Hu	SCLC
	Anti-recoverin	SCLC
Stiff person (anti-GAD) syndrome	Anti-amphiphysin	Breast

Key: VGCC, voltage gated calcium channel; SCLC, small cell lung cancer; anti-PCA-2; anti-purkinje cell antibody; anti-GAD, anti-glutamic acid decarboxylase antibody

Limbic encephalitis

- Short-term anterograde memory dysfunction
- Mood and sleep disturbances
- Acute confusional states
- Seizures may progress to partial status epilepticus

- Brain MRI reveals high FLAIR and T2 signal in mesial temporal lobe structures bilaterally
- CSF reveals mild pleocytosis and oligoclonal bands

Associated cancers
- Small-cell lung
- Testicular seminoma
- Thymoma
- Lymphoma

Differential diagnosis
- Herpes encephalitis
- Thiamine deficiency
- Vasculitis

Paraneoplastic syndromes: peripheral nervous system

Lambert-Eaton myasthenic syndrome (LEMS)
- Presynaptic disorder of the cholinergic neuromuscular and autonomic synapses
- Voltage-gated calcium channel antibody
- Associated with a malignancy in 60% of cases, usually small-cell lung cancer
- Forty percent autoimmune and not associated with malignancy
- Proximal weakness that may involve ocular muscles
- Weakness improves with continued use of muscle (facilitation)
- Autonomic involvement (dry mouth, orthostatic hypotension, impotence)
- EMG findings
  - Postexercise facilitation
  - Incremental response at 30 Hz
  - Reduced compound muscle action potential (CMAP) after single supramaximal stimulus
  - Single-fiber study demonstrates increased jitter.

Sensory neuronopathy
- Presents with painful progressive asymmetrical sensory neuropathy with propioceptive loss resulting in sensory ataxia
- No or little motor involvement
- May begin in arms
- NCV reveal axonal and demyelinating patterns

Differential diagnosis
- Metabolic neuropathy
- CIDP
- Vasculitis

Motor neuron syndromes

Clinical syndromes
- Anti-Hu-positive patients who go on to develop other paraneoplastic syndromes
- Breast cancer patients who develop a primary lateral sclerosis-like syndrome

Chapter 13

Neurotrauma

Stephen E. Sullivan, MD
Diana Gomez-Hassan, MD, PhD

Cranial trauma *346*
Management of traumatic brain injury (TBI) *349*
Management of specific head injuries *351*
Spinal trauma *356*

Cranial trauma

Epidemiology

- Trauma is the leading cause of death under age 45.
- Fifty percent of these deaths are due to traumatic brain injury (TBI).
- Fifty-two thousand deaths/year in the United States occur because of TBI.
- Fifty percent of TBIs are due to motor vehicle collisions.
- Alcohol is a factor in over 50% of TBI.
- Mortality for severe TBI (GCS <9) is 33%.
- Men are twice as likely as women to sustain TBI.

Pathophysiology

Primary injury

- Occurs at time of trauma
- Due to the following forces applied to the brain or surrounding structures:
  - Compressive: Tissue compression
  - Tensile: tissue stretch
  - Shear: tissues sliding past one another

Diffuse axonal injury

- Disruption of subcortical axons
- Mainly due to shear injury
- May be inferred from petechial hemorrhages in basal ganglia, corpus callosum (a marker of shear injury)

Intracranial hemorrhages

- Subdural hematoma: tearing of bridging veins
- Epidural hematoma: injury to meningeal artery
- Traumatic subarachnoid hemorrhage
- Contusions

Skull fractures

- Marker for point of impact
- Beware of underlying epidural hematoma

Penetrating brain injuries

- Gun shot wound
- Other penetrating missiles, e.g., shrapnel, nail gun injuries

Secondary injury

- Occurs hours to days after insult
- May be mediated by excitatory amino acids
- Increased intracranial pressure (ICP)
- Decreased cerebral perfusion pressure
- Hydrocephalus

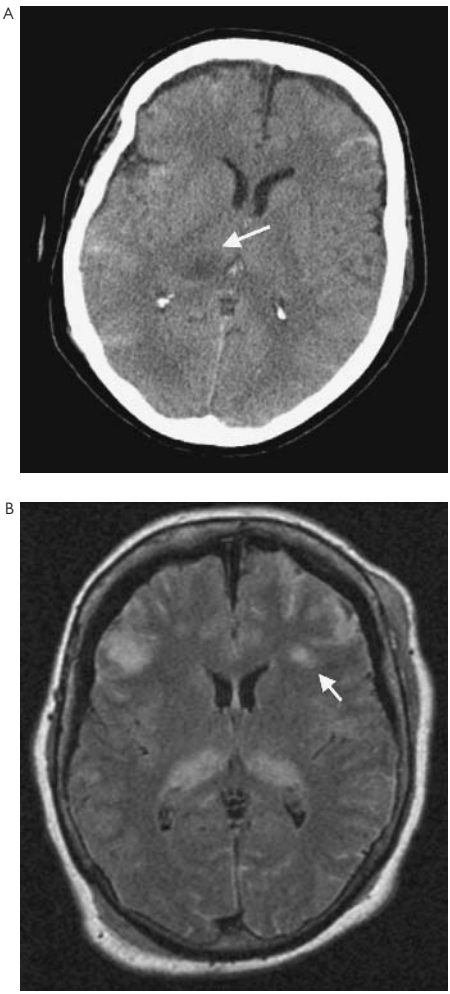

Figure 13.1 CT and MRI of parenchymal contusion and hemorrhage. Axial CT demonstrates areas of low attenuation in the right thalamus consistent (arrow) with parenchymal contusion. Subarachnoid hemorrhage is seen as high attenuation in the sulci (A). Both deep gray and white injury are seen as high FLAIR signal abnormalities in bilateral thalami, corpus callosum, and deep white matter (B). Deep white matter lesions are indicative of axonal injury.

Classificaton of TBI

- GCS 13–15: mild TBI
- GCS 9–12: moderate TBI
- GCS 3–8: severe TBI

Initial assessment

Advanced trauma life support protocol

- Secure airway
- Vigorous cardiovascular resuscitation
- Hypoxia and hypotension are poor prognostic factors.

Assess GCS (see Table 13.1)

- Emergent head CT if GCS <15 or focal neurologic abnormalities

Assess cervical spine

- Radiographs must be obtained if cervical pain is present or GCS <15.

Pertinent physical examination

- Hemotympanum
- Rhinorrhea
- Raccoon eye (periorbital bruising) and Battle sign (mastoid ecchymosis) indicate skull base fracture
- Spine tenderness, kyphosis, or spinous process "step off" (anterior or forward displacement of one spinous process relative to another, suggesting spinal subluxation)

Table 13.1 Glasgow coma scale (GCS)*

Score	Eye opening	Motor response	Verbal response
1	None	None	None
2	To pain	Extension	Sounds
3	To speech	Abnormal flexion	Words
4	Spontaneously	Flexion	Confused speech
5		Localizes	Orientated
6		Obeys commands	

* Note that the minimum GCS score is 3.

Management of traumatic brain injury (TBI)

Indication for head CT

- Abnormal sensorium, GCS <15
- Inebriated patient
- Focal neurological deficit
- Seizure
- Rhinorrhea
- Progression of symptoms

Hospitalization

- All patients with moderate and severe TBI (GCS <13) should be hospitalized.
- Selected patients with mild TBI and normal head CT can be discharged home with head injury instructions if a reliable adult can observe the patient.
- Intubate for
  - GCS <9
  - Worsening GCS
  - Insecure airway
  - Severe maxillofacial trauma
- Maintain head of bed >30%
  - Decreases ICP
- Frequent neurological checks by nursing and physicians
  - Stat head CT if neurological change occurs
- Intravenous fluids: 0.9% normal saline
  - Avoid hyponatremia and cerebral edema
- Control body temperature
  - Increased temperature may increase ICP

Mannitol

There is no role for prophylactic administration of mannitol unless the neurological examination is worsening or ICP is worsening.

Decadron

There is no role for steroids in TBI.

ICP monitoring

- Ventriculostomy is more accurate than intraparenchymal pressure transducer.
- Ventriculostomy allows treatment of high ICP by draining CSF.

Barbiturate coma

- May control ICP when other measures have been utilized to the maximum
- Titrate to burst suppression on EEG

Decompressive hemicraniectomy

- Aggressive treatment for high ICP unresponsive to other measures

Guidelines of the Brain Trauma Foundation

Hypoxia and blood pressure

- Maintain systolic blood pressure >90 mmHg
- Maintain O_2 saturation >90%

ICP monitoring

- ICP monitoring is recommended for all patients with GCS <9 and an abnormal head CT.
- Ventriculostomy is preferred.
- Maintain ICP <20 mmHg

Hyperosmolar agents

- Mannitol is effective in controlling increased ICP.
- Dose is 0.25 to 1.0 mg/kg
- Maintain euvolemia

Cerebral perfusion pressure

- Target range 50–70 mmHg
- Aggressive attempts to reach 70 mmHg associated with acute respiratory distress syndrome and worse outcome

Anticonvulsants

- Anticonvulsants should be discontinued 1 week after trauma unless late seizures develop.
- Prophylactic anticonvulsants do not decrease the development of late seizures (>1 week post trauma); they do decrease the risk of early seizures, but these are not correlated with worse outcome.

Hyperventilation

- Prophylactic hyperventilation worsens prognosis.
- There is a role for short-term hyperventilation as a bridge to definitive therapy (e.g.,on the way to the OR for subdural evacuation).

Prognosis

- GCS
  - GCS 3–5 = 80% dead or with severe disability
  - GCS 6–8 = 30% dead or with severe disability
  - GCS 9–13 = 15% dead or with severe disability
- Increasing age
  - Worsens prognosis
- Pupillary reflex
  - Bilaterally nonreactive pupils associated with death or vegetative state in ~90% of cases
- Hemodynamic
  - Hypotension and hypoxia worsen outcomes

Management of specific head injuries

Space-occupying lesions

- Expanding mass lesions require emergent attention.
- Initially, cerebral hemispheric compression causes contralateral focal signs followed by mental status depression and finally ipsilateral 3rd nerve palsy due to uncal herniation.
- This will progress to transtentorial herniation causing motor posturing (decerebrate rigidity) and absent brainstem reflexes
- May result in Cushing response (bradycardia and hypertension)
- False localizing sign: hemiparesis ipsilateral to the lesion may occur due to cerebral peduncle compression on edge of contralateral tentorium (Kernohan notch)

Epidural hematoma (EDH)

- A coup injury (ipsilateral to direct trauma)
- Cause is tear of meningeal artery often due to fracture
- Classically associated with initial loss of consciousness, then normal sensorium (lucid interval) followed by deteriorating mental status
- May rapidly deteriorate

Imaging

- CT: biconvex ("lentiform") high-density extra-axial hemorrhage that does not cross suture lines
- Often underlying a skull fracture
- Fifty percent associated with a contrecoup injury

Management

- True neurosurgical emergency
- Intubate and infuse mannitol prior to surgery if deteriorating before neurosurgical care is available
- Emergency frontotemporal craniotomy

Prognosis

- Depends on preoperative GCS
- Excellent prognosis if patient is conscious prior to surgery

Acute subdural hematoma

- Typically occurs from high-energy trauma unless the patient has a coagulopathy
- Highest mortality of posttraumatic mass lesions
- Immediate LOC with progressive neurological decline
- The underlying brain injury is often out of proportion to the size of the subdural hematoma.
- The hemorrhage occurs from damage to cortical vessels or bridging veins.

Imaging

- CT: hyperdense crescentric mass. May cross suture lines and extend along falx cerebri and tentorium
- Hyperacute bleeding may cause low-density appearance on CT

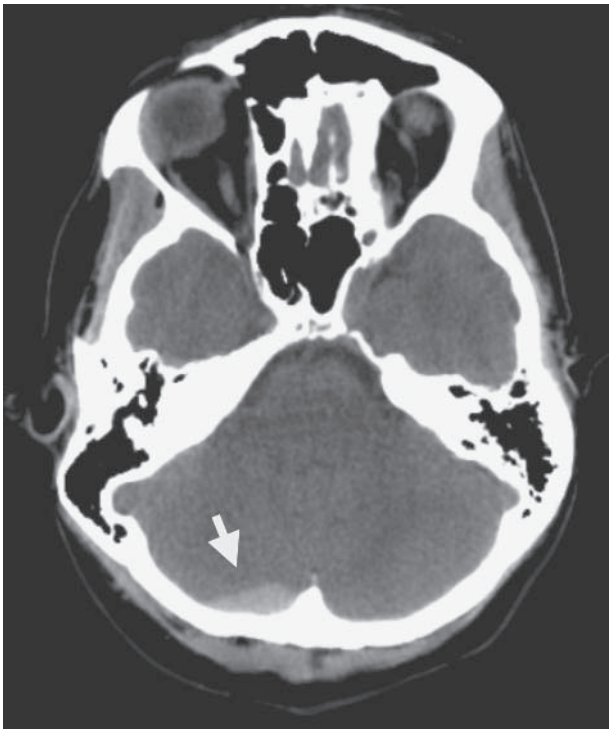

Figure 13.2 Noncontrast head CT of right posterior fossa epidural hematoma demonstrating lentiform shape and high-attenuation acute blood.

Management

- Indications for emergent surgical management include any of the following:
  - Progressive neurological deterioration
  - Subdural thickness greater than 1 cm
  - Midline shift greater than 5 mm
  - Increased ICP

Procedure

- Large frontotemporoparietal craniotomy
- Bone flap left off if significant cerebral edema
- ICP monitoring often indicated

Outcome
- In general worse than extradural hematoma
- Depends on presenting GCS and underlying brain injury
- Good outcome 30%
- Mortality 50%

Chronic subdural hematoma
- Late sequelae of mild to moderate head injury; up to 50% do not remember an obvious head injury
- Risk factors are advanced age, alcoholism, and coagulopathy
- Clinical course often insidious and includes the following:
  - Cognitive changes
  - Gait dysfunction
  - Focal neurological symptoms
  - Transient neurological symptoms
  - Headache

Imaging
- CT: low to iso-intense hemispheric extra-axial fluid collection

Management
- Small asymptomatic chronic SDH may be observed with serial head CT to allow self-resolution.

Indications for surgery include
- Symptomatic SDH
- Midline shift
- Progressive increase in size on serial head CT
- Pressing need to restart anticoagulation

Procedure
- Most respond to burr hole drainage with subdural drain
- Recurrence rate 15%
- Complications include seizures, pneumocephalus, and subdural empyema

Traumatic intracerebral hematoma (cerebral contusion)
- Small contusions may progress to significant ICH.
- Most do not require surgical evacuation
- Indications for surgical evacuation are progressive neurological deficit or uncontrolled increase of ICP.
- May be result of coup or contrecoup injury
- ICH does not change the recommendation for 1 week of anticonvulsant treatment.

Penetrating head injuries
- Mortality from gunshot wounds (GSW) higher than 50%
- Bihemispheric GSW usually fatal

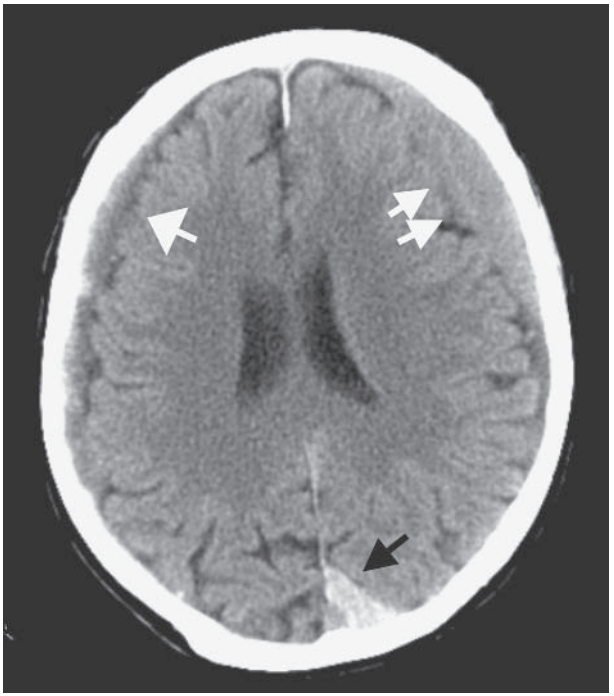

Figure 13.3 Noncontrast head CT of multiple subdural hematomas of varying ages. Chronic subdural hematomas demonstrate CT attenuation below that of brain (single white arrow, right frontal). Subacute hematomas are isointense to brain (double white arrows left frontal), and acute subdurals demonstrate high attenuation (black arrow, left occipital).

Significant risk of

- Infection/abscess
- CSF leak
- Vascular injury (especially if trajectory crosses Sylvian fissure or interhemispheric fissure)

Management

- Begin anticonvulsants and antibiotics
- Angiogram should be performed on anyone with bullet trajectory near vascular structures.
- Salvageable patients should undergo urgent craniotomy.

Goals of surgery

- Debride and irrigate surface contaminants (bone, contaminants from skin)
- Prevent CSF leak
- The bullet fragment is not retrieved unless it is found just at cortical surface, then given to police officer following strict chain of evidence guidelines
- Evacuation of large ICH
- Elevation of significantly depressed skull fractures
- Consider leaving off bone flap to treat high ICP

Diffuse axonal injury

- Injury to subcortical axons due to shear injury
- Usual cause of coma in patients with no mass lesion
- May lead to persistent vegetative state if severe
- May cause cerebral edema

Imaging

- CT: normal or petechial hemorrhages in deep cerebral structures
- MRI: multiple high FLAIR and T2 abnormalities in corpus callosum, basal ganglia, and brainstem

Management

- ATLS protocol
- ICP monitoring and control

Basal skull fractures

Clinical features

- Raccoon eyes, Battle sign
- Rhinorrea
- Cranial neuropathies
- Carotid dissection

Management

- Most do not need surgical treatment.
- Most CSF leaks spontaneously heal in 1 week; if not, consider lumbar drain and/or surgery.
- Avoid prophylactic antibiotics for CSF leak
- Orbital injuries may need surgical decompression.
- Severe maxillofacial trauma may need a combined neurosurgical approach with otolaryngology, plastic surgery and/or ophthalmology.
- Nasal tubes are contraindicated with frontobasilar fractures.

Delayed complications

- Vascular
  - Carotid/vertebral artery dissections
  - Traumatic aneurysms
  - Carotid cavernous fistulae
  - Chronic SDH

- Infections
  - Cerebral abscess
  - Subdural/epidural empyema
  - Meningitis
- Epilepsy
  - Occurs in 2.5% of all TBI patients
  - Occurs in 10%–15% of severe TBI patients
  - Incidence of posttraumatic epilepsy not affected by prophylactic anticonvulsant use
- Cranial nerve deficit
  - Loss of olfaction is the most common.
  - Vesticulocochlear injury with posttraumatic vertigo
  - Facial paresis
  - Trigeminal injury
- Behavioral abnormalities, headaches, and depression

Spinal trauma

- Often associated with multiple injuries and head trauma
- Early immobilization in the field and early detection are critical.

Complete lesion refers to the complete lack of motor and/or sensory function below the level of the lesion.

Incomplete lesion refers to some degree of motor and/or sensory function below the lesion.

Spinal level is defined as the lowest level of normal motor and sensory function.

Spinal shock refers to hemodynamic effects and motor flaccidity noted early after some cervical spine injuries, may last 1–2 weeks.

Spinal stability

Instability is defined as loss of maintenance normal anatomical spinal alignment under normal physiologic loads.

Thoraclumbar stability is classified according to the Denis three-column model:

- Anterior column: anterior one-half of the vertebral body plus annulus fibrosis and anterior longitudinal ligament
- Middle column: posterior one-half of the vertebral body plus annulus fibrosis and posterior longitudinal ligament
- Posterior column: pedicles plus laminae, spinous processes, and dorsal ligaments

The spine is unstable if two or three columns are disrupted.

Acute cord injury

Management

- Resuscitation and airway protection
- Immobilization of the neck and log roll precautions during assessment

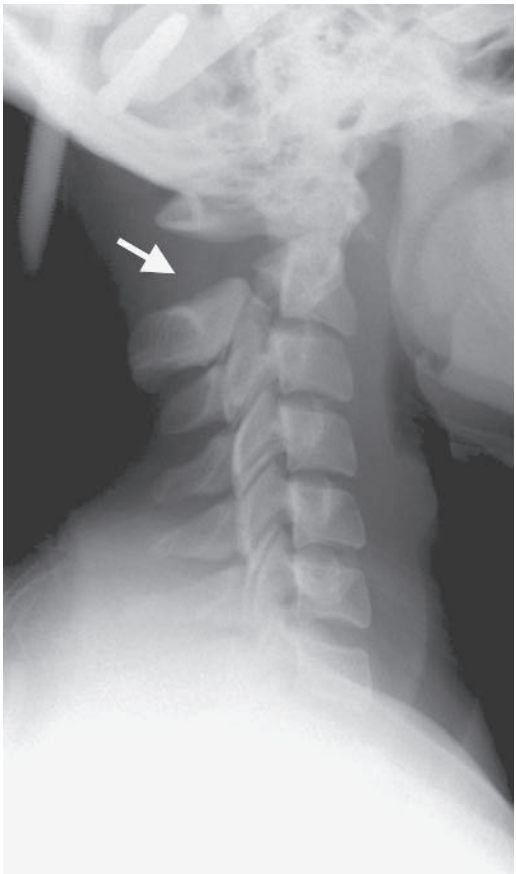

Figure 13.4 Lateral cervical spine X-ray of a traumatic fracture subluxation of C2 (hangman fracture). White arrow points to the pars interarticularis of C2, which can be followed ventrally to identify the fracture. Please note the subluxation of C2 on C3.

- Treatment of life-threatening injuries and bleeding
- Full neurological examination to determine level and completeness of lesion
- Palpate spine for step off
- Note any autonomic dysfunction, e.g., priapism, ileus

- IV methylprednisolone may improve outcome of injury if given within 8 hours but increases risk of pneumonia and gastrointestinal complications.

Occipital cervical dislocation

- Often fatal
- Clinical signs include lower cranial neuropathies, motor dysfunction, and basilar subarachnoid hemorrhage
- Sagittal CT of cervical spine will demonstrate widened or dislocated C1-occipital condyle joint. MRI may show blood in this joint and disruption of tectorial membrane

C1 fracture (Jefferson fracture)

- Axial loading injury resulting in multiple fractures of the ring of C1
- Nearly half are associated with a C2 fracture.
- Most patients are neurologically intact.

Imaging

- CT has the most diagnostic utility, will reveal fracture of ring of C1 in up to four points
- MRI is useful to determine whether the transverse ligament is intact.
- Open-mouth X-rays suggest an intact transverse ligament if the overhang of the sum of both lateral masses is 6 mm or less (rule of Spence).

Management

- "Stable" Jefferson fracture (transverse ligament intact) may be treated in an external orthosis like the Miami J collar for 3 months.
- "Unstable" Jefferson fracture (transverse ligament disrupted) may be treated in a halo orthosis for 3 months or internally fixated surgically.

C2 fracture (odontoid fracture)

Classification

- Type I: upper dens fracture (10%)
- Type II: base of neck and peg (60%)
- Type III: transverse fracture through C2 vertebral body (30%)

Clinical features

- Neck pain usually present
- Neurological injury is found in 20% of type II injuries

Imaging

- Cervical CT: most diagnostic
- MRI: useful for analysis of ligaments and spinal cord
- Open-mouth and lateral X-rays may be difficult to interpret

Management

- Type III: external orthosis
- Type II: halo or internal fixation (odontoid screw or C1, 2 fixation)
- Surgical intervention indicated when
  - Peg displacement is >4 mm
  - Persistent movement occurs when patient is immobilized in halo
  - Symptomatic fibrous nonunion
  - Comminuted C2 fracture

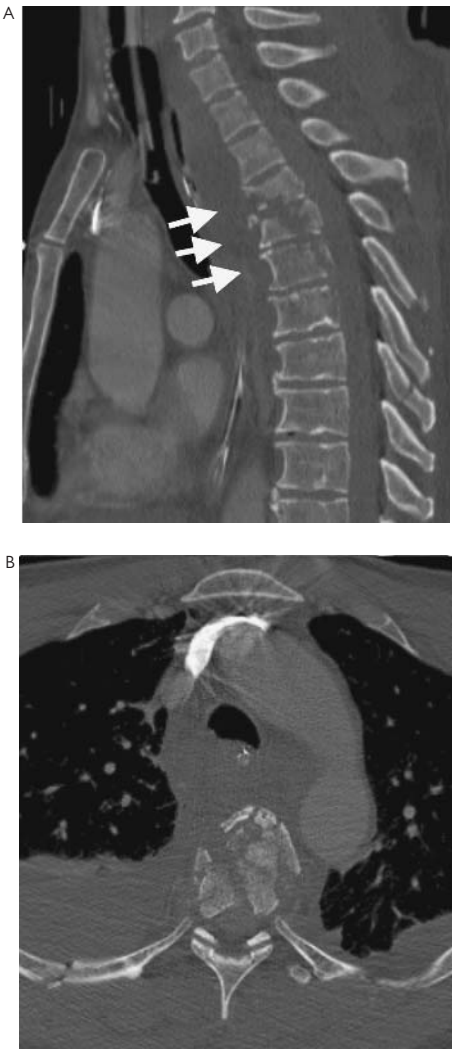

Figure 13.5 Nonenhanced CT of multiple thoracic spinal fractures. Sagittal reconstructions (A) shows severe oblique fractures over multiple upper thoracic segments (arrows). Burst vertebral, bilateral rib fractures, mediastinal hematoma and bilateral pleural collections are seen on an axial image (B).

Hangman fracture

High-impact axial load, traumatic spondylolisthesis of C2 due to fracture of the pars interarticularis

Clinical features

- Most patients are neurologically intact
- Neck pain

Imaging

- Usually evident on lateral c-spine X-ray
- CT is most sensitive

Management

- Most are treated with immobilization in a halo.
- Indications for surgical fixation
  - Misalignment despite gentle traction and manipulation in awake intact patient
  - Movement in halo
  - Nonunion after 3 months of immobilization in halo

Subaxial fractures (C3–C7)

Commonly associated with head injuries and severe neurological deficit

Clinical features

- Neck pain
- Radiculopathy
- Brown Séquard syndrome
- Quadriplegia
- Central cord syndrome (arm > leg weakness)

Imaging

- AP/lateral c-spine X-rays reveal most significant injuries, may need swimmer's view for lower c-spine
- CT more sensitive
- Flexion-extension films are only done on neurologically intact awake patients with no skeletal injury to investigate ligamentous injury.
- MRI useful to evaluate ligamentous injury and spinal cord

Cervical facet dislocation

- Flexion injury resulting in superior facet on one or both sides moving forward and "locking" on inferior facet
- High-energy injury
- Associated with significant dorsal ligamentous injury

Clinical features

- Usually associated with a severe spinal cord injury, especially if bilateral
- Spinal shock
- Unilateral facet dislocation: 25% intact neurologically/65% partial spinal cord injury/10% complete spinal cord injury

Imaging

- Lateral c-spine will show facet dislocation

Figure 13.6 Direct impact (nonenhanced CT). Blunt trauma to the right frontal region with extracranial soft tissue swelling (open white arrowheads) and right frontal fracture (closed white arrow). There is an extensive underlying parenchymal contusion comprising low attenuation components (closed white arrowheads) and central hemorrhagic change (open white arrows). There is associated mass effect with ipsilateral sulcal and ventricular effacement and minor distortion of the midline. Note also the small right frontal extradural hematoma (black arrow).

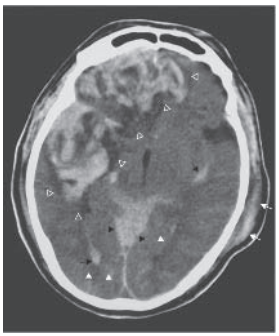

Figure 13.7 Indirect impact (nonenhanced CT). Blunt trauma to the left temporoparietal region (white arrows) with sudden cranial deceleration and angular rotation resulting in shear–strain forces causing large hemorrhagic "contre-coup" contusions in the inferior aspects of both frontal and right temporal lobes (open white arrowheads). Note also smaller foci of parenchymal hemorrhage in the occipital lobe bilaterally (closed white arrowheads), intraventricular and subarachnoid blood (black arrows), and an extensive tentorial subdural hematoma (black arrowheads).

- Subluxation of ~25% vertebral body is associated with unilateral facet dislocation
- Subluxation of ~50% is associated with bilateral facet dislocation
- AP films show rotatory subluxation in unilateral facet dislocation
- MRI useful to identify traumatic disc rupture or spinal epidural hematoma

Management

- Subluxation can be reduced with cervical traction in skull tongs if patient is awake and can be examined, maximum of 5 lb per vertebral body level of fracture
- Open reduction in the operating room if this fails
- The majority require surgical internal fixation once the spine is realigned

Thoracolumbar fractures

- Caused by high force
- Associated with other visceral injuries, e.g.,aortic tear, sternal fracture

Classification

- Wedge: anterior column
- Burst: anterior and middle column
- Fracture dislocation: all columns

Clinical features

- Back pain
- Neurological deficit common

Imaging

- CT most sensitive for skeletal injury
- MRI for cord compression

Management

- Complete neurological deficit: proceed to internal fixation early to mobilize patient and reduce complications
- Incomplete neurological deficit: emergent decompression and internal fixation
- Unstable injury with no deficit: early internal fixation

Chapter 14

Neurosurgery

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Diana Gomez-Hassan, MD, PhD

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Degenerative spinal conditions: cervical spine

Cervical degenerative disease is common, but care needs to be taken to distinguish pathological conditions from changes due to aging.

- More than 95% of individuals >65 years will have MRI scan abnormalities

Cervical spondylosis

Nonspecific degenerative process resulting in stenosis of the spinal canal and or root canals. Factors include the following:

- Degenerate disc
- Osteophytes
- Hypertrophy of lamina, articular facets, ligamentum flavum, and posterior longitudinal ligament
- Congenitally narrow canal

Most common levels affected are C5/C6 and C6/C7.

Mechanical/musculoskeletal neck pain

No root symptoms or signs. Management involves the following:

- Lifestyle and posture changes (occupational therapy)
- Anti-inflammatory drugs
- Physiotherapy
- Judicious use of a collar
- Facet joint or epidural injection of LA/steroids
- Surgery rarely indicated

Radiculopathy

Clinical features

- Referred pain in the arm due to root irritation (brachalgia)
- Initial symptom may be sensory (tingling, burning) in a dermatomal distribution followed by radicular pain (which is in a myotomal pattern)
- Weakness
- Reflex abnormalities
- See Table 14.1.

Table 14.1 Clinical presentation of cervical radiculopathies

Nerve root (disc level)	Pain	Motor weakness	↓ Reflexes	Sensory disturbance
C5(C4/C5)	Neck to shoulder and upper arm	Deltoid, supra + infraspinatus	Supinator	Shoulder, lateral arm
C6(C5/C6)	Lateral forearm, thumb, and index finger	Biceps and brachioradialis	Biceps	Lateral forearm, thumb, and index finger
C7(C6/C7)	Posterior arm, dorsum, forearm, middle finger	Triceps, wrist and finger extensors	Triceps	Posterior forearm, middle finger
C8(C7/T1)	Shoulder medial forearm, ring and little fingers	Thumb flexor, intrinsic hand muscles		Medial hand, ring and little fingers

Degenerative spinal conditions: thoracic and lumbar spine

Thoracic disc prolapse

Symptomatic disc prolapses are rare, <1% of all protruded discs. Most common level T11/T12.

Clinical features

- Pain localized to the spine or radicular. Nocturnal recumbent pain typical
- Sensory symptoms and signs with a sensory level
- Spastic paraparesis or rarely a monoparesis
- Sphincter disturbance
- Rarely, a Brown–Sequard syndrome

Imaging

MRI for location, severity of cord compression, and associated myelomalacia

Management

- Radicular pain managed with analgesics and/or local nerve root block. Surgery if intractable
- Progressive or significant myelopathy or sphincter dysfunction an indication for surgery. If disc is heavily calcified or located midline anterior, transthoracic approach is used. Posterior approach used for lateral and soft anterolateral discs—usually a fusion procedure carried out to ensure spinal stability

Lumbar intervertebral disc prolapse

- Acute back pain is common but accompanied by sciatica in only 2%.
- L5/S1 disc and L4/5 disc prolapses account for >95%

Clinical features

- Acute or gradual onset pain in the back radiating through buttock, thigh, leg to foot. L2 radiculopathy (unusual) causes anterior thigh pain. Triggered by lifting, flexion, or rotation. Dull ache with shooting exacerbations. Increased with coughing, sneezing, bending, or prolonged sitting
- Weakness of ankle dorsiflexion and EHL (L5); plantar flexion (S1); knee extension (L3, L4)
- Depressed or absent knee jerk (L3, L4); ankle jerk (S1)
- Straight leg raising (Lasegue sign) causes dermatomal pain.
- Positive femoral stretch test (hip extension with maximal knee flexion) indicates L2, L3, or L4 root pathology. Other causes: psoas abscess or hematoma
- Cauda equina syndrome (neurosurgical emergency)
  - Bilateral leg pain or sensory disturbance
  - Perianal, perineal, and saddle anaesthesia
  - Urinary and/or faecal incontinence
  - Low back pain
  - Sexual dysfunction
  - Bilateral motor and reflex deficits

Imaging

- MRI is the investigation of choice.
- CT or CT myelogram is a useful alternative.
- Most commonly a posterolateral prolapse will compress root just proximal to exit foramen, e.g., L4/L5 disc compresses L5 root. However, the L4 root will be affected by upwardly migrated L4/L5 disc fragment or a far lateral disc protrusion.

Management

Acute back pain and 85% of sciatica resolve in 6–8 weeks with conservative treatment. Note: exclude infection and tumor first.

- Initial bed rest, early mobilization
- Avoid bending, lifting, prolonged sitting
- Adequate analgesia
- Muscle relaxants, e.g., diazepam 2–5 mg
- Consider epidural or nerve root block

Indications for surgery

- Cauda equina syndrome
- Significant or progressive motor deficit
- Severe pain not responding to conservative measures

Surgery involves microdiscectomy. Recurrent disc herniation rate is 2%. Recurrence of symptoms may also be due to scarring around nerve root. MRI with Gd shows root enhancement.

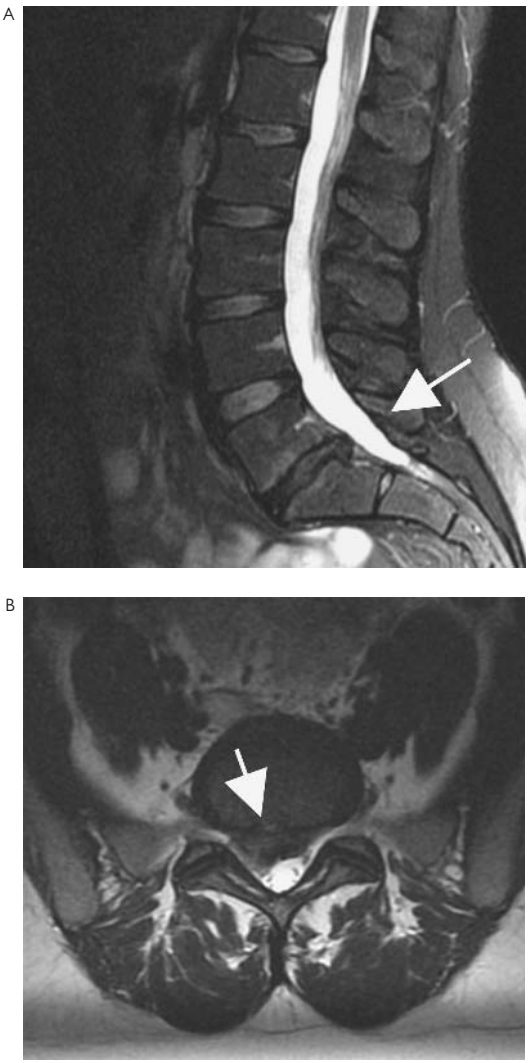

Figure 14.1 T2-weighted MRI of disc herniation: sagittal (A) and axial (B). L5-S1 paracentral disc herniation (white arrows) causing compression of the left S1 nerve root (B).

Lumbar canal stenosis

Narrowing of the spinal canal in the central, lateral recesses or intervertebral foraminae causing root compression. Most common: L4/5 and L3/L4.

Clinical features

- "Neurogenic claudication": buttock and leg pain or motor deficit on walking, standing, or lying supine. Alleviated by bending forward or crouching. Exercise tolerance improved by cycling or pushing a trolley
- Usually bilateral but may affect only one leg
- Leg numbness or paraesthesiae
- Occasionally sphincter dysfunction or impotence
- Neurological examination may be normal.

Figure 14.2 Sagittal T2-weighted MRI of spinal stenosis. Severe multilevel cervical stenosis (white arrows) causing spinal compression. Note the high T2 signal within the cord at C3,4 and C5,6 consistent with spinal cord injury.

Imaging

- MRI investigation of choice: bilateral facet hypertrophy. Lateral recess stenosis results in a trefoil deformity on axial scans.
- CT or CT myelography is useful if MRI contraindicated or not available.
- Lateral flexion/extension views indicated to exclude spinal instability as fusion may be necessary at decompression

Management

Mild symptoms: conservative management

- Rest
- Adequate analgesia
- Lumbar corset
- Physiotherapy for posture and trunk strengthening
- Epidural steroid/LA injections reported to result in long-term benefit

Surgery indicated if:

- Failure of conservative measures
- Pain
- Significant motor deficit
- Sphincter disturbance

Decompressive surgery consists of variations on lumbar laminectomies.

- If spondylolisthesis (AP slip of one vertebra on another) or instability, fusion procedures performed
- Complications: dural tear and CSF leakage

Developmental abnormalities

Arachnoid cysts

Congenital CSF-containing cysts developing between arachnoid layers. Fifty percent in the middle cranial fossa, 10% suprasellar, 10% cerebellopontine angle. Less common sites include quadrigeminal cistern, hemispheric convexity, and the posterior fossa.

Clinical features

- Majority present in childhood
  - Middle cranial fossa: seizures, headache, hemiparesis
  - Suprasellar cysts: hydrocephalus, enlarged skull, developmental delay, visual failure, and precocious puberty
- In adults, incidental finding

Imaging features

Sharply demarcated cysts, which may have mass effect. May communicate with the subarachnoid space. Walls are indefinable.

- CT: CSF density with no enhancement. Typically, remodeling and scalloping of adjacent walls is evident. Hemorrhage (rare)
- MRI: CSF signal intensity on all images. Null signal on FLAIR. DWI images show free diffusion in contrast to epidermoid cysts, which show restricted diffusion with increased signal. Other differential diagnoses: cystic extra-axial tumor (usually has a wall, a solid component with enhancement); cysticercosis; mega cisterna magna in the posterior fossa

Management

- If asymptomatic, no treatment
- Symptomatic cysts drained either via a marsupialization into CSF spaces (via a craniotomy or endoscopy) or via a shunt to the peritoneum

Chiari malformation

Syndromes of hindbrain descent. four subtypes are probably unrelated. Types 1 and 2 predominate.

Chiari 1 malformation (cerebellar ectopia)

Anatomy

Simple descent of cerebellar tonsils beyond the foramen magnum. Elongated peg-shaped tonsils plug the foramen. Occasionally acquired after LP. Cerebellar descent and arachnoid adhesions interfere with normal transmission of CSF pressure waves across the FM to the spinal reservoir, raising ICP and forcing fluid into the central canal of the spinal cord.

Clinical features

Usually presents in young adults.

- Suboccipital headache, increased with stooping, straining, coughing
- Brainstem compression with ataxia, lower cranial palsies, pyramidal weakness
- Central cord syndrome due to the associated syringomyelia with dissociated sensory loss in a cape distribution. Downbeat nystagmus

Management

Foramen magnum decompression by removal of 3 x 4 cm crescent of bone from the posterior rim of FM. Restores CSF pathway and decompresses syrinx. Complications: aseptic meningitis, CSF leak, hydrocephalus.

Chiari 2 malformation

Anatomy

Congenital hindbrain abnormality associated with spinal dysraphism (myelomeningocele, spina bifida). Descent of cerebellar tonsils, vermis, medulla, fourth ventricle through FM. Associated with hydrocephalus and elongated upper cervical nerves.

Clinical features

Present in infancy with the following:

- Hydrocephalus
- Respiratory distress
- Dysphagia and aspiration pneumonia
- Downbeat nystagmus
- Quadraparesis

High mortality from respiratory arrest.

Imaging features

MRI: S-bend medulla, tonsillar descent, large interthalamic connexus, dysgenesis of corpus callosum, hydrocephalus, medullary compression, syringomyelia.

Figure 14.3 Sagittal T1-weighted brain MRI of Chiari I malformation demonstrating cerebellar tonsilar ectopia (black arrow) down to the ring of C1.

Management

- Insertion of ventriculo-peritoneal (VP) shunt for hydrocephalus
- Posterior fossa decompression

Dandy–Walker malformation

- Agenesis of the vermis of the cerebellum, resulting in a large posterior cerebellar cyst opening into the fourth ventricle
- Hydrocephalus is common.
- Associated with agenesis of the corpus callosum, occipital encephalocele, spina bifida, syringomyelia
- Facial, ocular, and cardiovascular abnormalities

Management Insertion of a cyst-peritoneal shunt and/or ventriculo-peritoneal shunt.

Aqueduct stenosis

Congenital aqueduct stenosis presents in childhood with hydrocephalus in the first 3 months of life. Adult forms usually acquired due to inflammation, infection, brainstem tumor, arachnoid cysts.

Clinical features

- Symptoms and signs of increased ICP
- Cognitive impairment
- Visual field deficit
- Ataxia
- Incontinence

Management

- Insertion of a VP shunt
- Endoscopic third ventriculostomy (by creation of a hole in the floor of the third ventricle allowing CSF to reach the basal cisterns bypassing the aqueduct and fourth ventricles)

Spinal dysraphism (spina bifida)

Developmental defects of neural tube closure with a variety of abnormalities:

- Spina bifida occulta. Often clinically insignificant finding of hypoplastic posterior sacral elements with normal dural sac and skin cover. May have skin stigmata: hairy patch, naevus. Associated with intradural

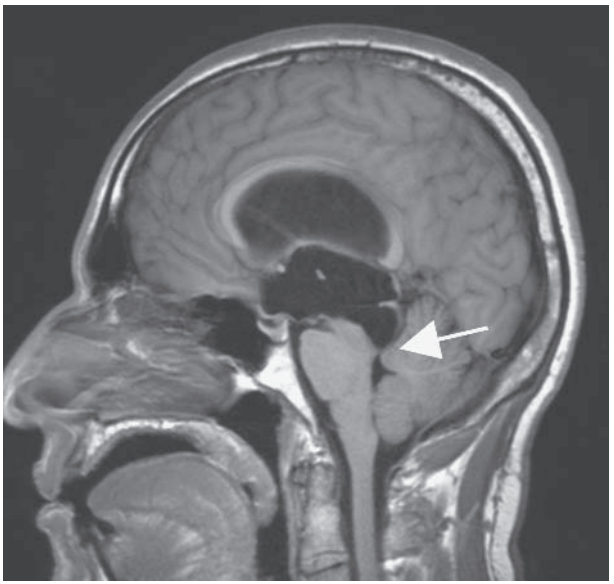

Figure 14.4 Sagittal T1-weighted brain MRI of hydrocephalus due to aqueductal stenosis. An aqueductal web (white arrow) causes supratentorial hydrocephalus and severe dilatation of the proximal aqueduct. Note the nondilated fourth ventricle.

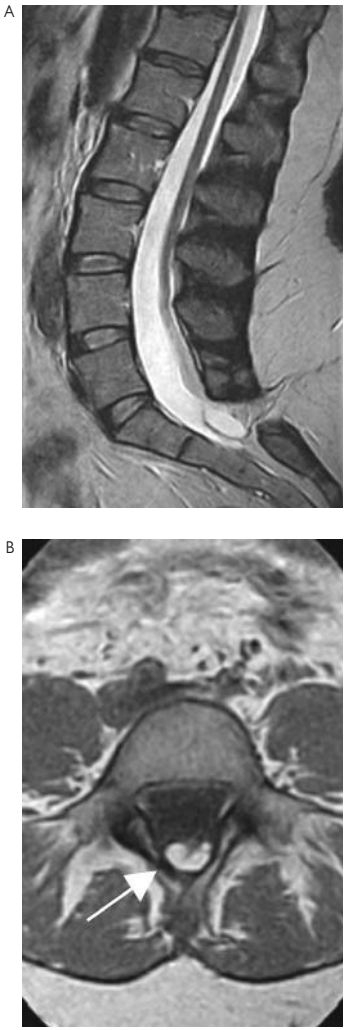

Figure 14.5 Sagittal T2-weighted (A) and axial T1-weighted (B) MRI of lumbar spine. Tethered spinal cord at upper sacral segments due to congenital lipomyelomingocele. The conus medullaris ends at L5 (A). The high-signal lipoma can be seen in B (white arrow).

lipomas, thickened filum terminale, diastematomyelia (split cord), and dermoid cysts. Cause of tethered cord syndrome
  - Neurogenic bladder
  - Paraparesis
  - Foot deformity
- Meningocele. Developmental absence of sacral and low lumbar posterior elements with bulging meninges exposed at skin surface. Neurological deficit in 30%
- Myelomeningocele. Congenital absence of posterior vertebral elements, dura and maldevelopment of the terminal spinal cord. All have a neurological deficit with, hydrocephalus in 80%. Associated with Chiari 2 malformation

Management

Myelomeningocele requires early closure to decrease infection rate and protect neural tissue from damage. Hydrocephalus may be apparent after closure and treated with a VP shunt. With surgery 85% survive infancy, most with normal IQ.

Syringomyelia

Caused by cavitations within the spinal cord with clinical deficits. May coexist with a similar condition, syringobulbia. Due to abnormal CSF circulation resulting from anatomical abnormalities.

Causes

- Cerebellar ectopia (Chiari malformations)
- Intramedullary tumors
- Trauma

Clinical presentation

Usually early to mid adult life with:
- Cough and positional headache due to pathology at FM
- Lower motor neuron weakness in the hands and arms, e.g., wasted hand + paraparesis of the legs
- Dissociated sensory loss (cape distribution) affecting spinothalamic sensation but sparing posterior columns

Imaging features

Cranial and spinal MRI + Gd. Assessment of the craniocervical junction; presence of any cord tumors.

Management

The natural history is unclear. Medical treatment based on physiotherapy, occupational therapy, and pain management.

Surgery

- Decompression of the FM. May arrest and sometimes reverse progression of syringomyelia

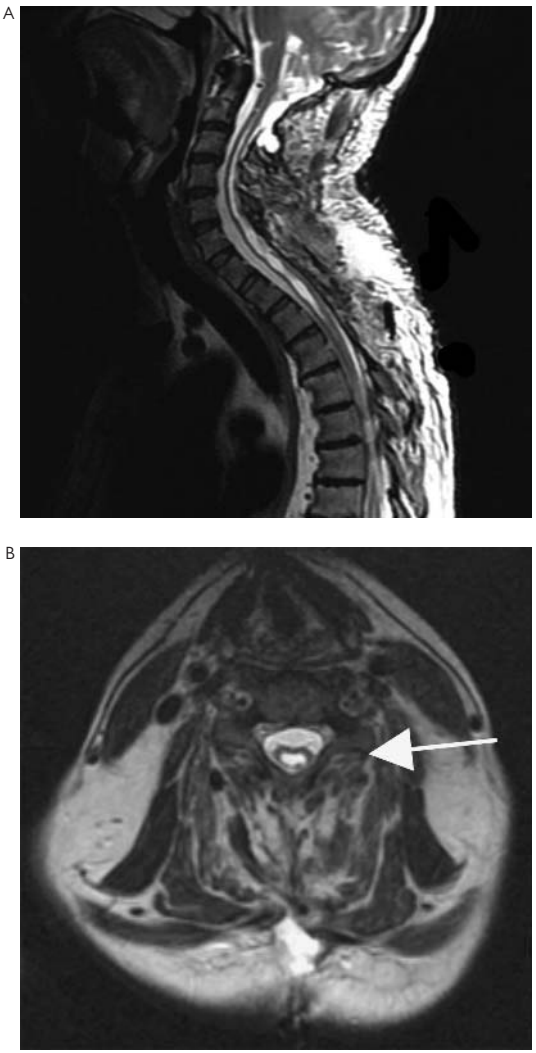

Figure 14.6 Sagittal T2-weighted MRI of cervical spinal cord syringomyelia. Note dilation of the syrinx up to the level of the obex. Diffuse atrophy of the cord is also noted.

- Syrinx cavity operations consist of a drainage procedure usually in cases of progressive neurological deficits
  - Syringo-arachnoid shunt
  - Syringo-pleural shunt

Revision procedures often required.

Hydrocephalus

- Defined as an excessive accumulation of CSF caused by a disturbance of formation, flow, or absorption
- Normal CSF production is 500 mL/24 hr
- Total CSF volume in an adult is 120–150 mL
- CSF is recycled 3× daily

Types of hydrocephalus

- Communicating hydrocephalus. Enlarged ventricles with preserved CSF flow between ventricles and the subarachnoid space. Impaired CSF reabsorption results in increased CSF pressure and ventricular enlargement.
- Noncommunicating hydrocephalus or obstructive hydrocephalus occurs when CSF outflow tracts are obstructed, e.g., exit foraminae of the fourth ventricle (Magendie and Luschka)
- Hydrocephalus ex vacuo refers to compensatory ventricular enlargement secondary to brain atrophy.
- Arrested hydrocephalus occurs usually in communicating hydrocephalus due to incomplete obstruction when CSF production is balanced by absorption. The CSF pressure may be normal. However, patients may undergo decompensation spontaneously or after a minor head injury.
- Normal-pressure hydrocephalus is a condition with low-grade hydrocephalus with intermittently raised ICP.

Acute hydrocephalus

Etiology

- Posterior fossa tumors
- Cerebellar hemorrhage or infarction
- Colloid cyst of the third ventricle
- Ependymoma of the fourth ventricle
- SAH
- Trauma
- Acute meningitis

Clinical features

- Signs and symptoms of increased ICP
- Headache
- Vomiting
- Diplopia due to sixth nerve palsies

- Reduced upgaze
- Impaired conscious level
- Occasionally, especially with colloid cyst of the third ventricle, LOC and sudden death

Chronic hydrocephalus

Etiology

- SAH
- Chronic meningitis
- Slow-growing posterior fossa tumors
- One-third of cases have no obvious cause.

Clinical features

- Gait disturbance (apraxia)
- Memory disturbance or dementia
- Urinary incontinence
- Symptoms and signs of increased ICP

Imaging features in hydrocephalus

CT/MRI features include the following:

- Ventricular enlargement with ballooning of frontal horns
- Enlargement of temporal horns
- Ballooning of the third ventricle
- Disproportionate enlargement of ventricles compared to sulci (neuroradiological expertise necessary)
- Periventricular interstitial edema
- Thinned or upward bowing of corpus callosum on sagittal MRI
- A large fourth ventricle implies communicating hydrocephalus or obstruction at the level of the fourth ventricular outflow; a small fourth ventricle suggests aqueduct stenosis.

Congenital causes (may present with acute or chronic hydrocephalus):

- Aqueduct obstruction
- Arnold–Chiari malformation
- Dandy–Walker syndrome
- Benign intracranial cysts

Management

- Insertion of ventricular peritoneal (VP) shunt inserted via a frontal or parietal burr hole. Attached to a combined valve and reservoir connecting to a distal catheter tunneled under the skin and implanted into the peritoneum
- Alternative sites: ventriculopleural shunt; ventriculo-(right) atrial (VA) shunt. Both have a higher complication rate than VP shunt, e.g., pulmonary emboli in VA shunts
- Programmable shunt valve with variable settings that may be changed by application of magnetic device to skin

- Endoscopic third ventriculostomy. Creation of a hole in the floor of the third ventricle allowing CSF to escape from the ventricular system to the basal cisterns. Endoscope introduced into the anterior horn of the lateral ventricle via a frontal burr hole, passed through the foramen of Munro into the third ventricle and a hole punched anterior to tuber cinereum
- In communicating hydrocephalus, e.g., due to acute meningitis, serial LP, or an external lumbar drain may suffice in the acute period. A CSF protein level >4 g/L will clog most shunts.

Normal pressure hydrocephalus (NPH)

- NPH describes a syndrome of chronic communicating hydrocephalus with normal CSF pressure at lumbar puncture.
- Long-term pressure monitoring reveals intermittently elevated pressures, often at night.
- NPH may follow trauma, infection, or SAH.
- Majority are idiopathic

Clinical features

Presentation with some or all features of the classical Adam's triad.

- Gait disturbance. Typically the gait is an apraxia, i.e., normal power and sensation, but with an inability to lift the legs to walk. However, performance of the bicycling maneuver on the bed is remarkably intact.
- Cognitive impairment. Gradual slowing of verbal and motor responses and patients may seem apathetic or depressed
- Urinary incontinence

Additional symptoms may include drop attacks and brief episodes of LOC.

Imaging features

- CT. Enlarged ventricles including temporal horns but with normal sulci
- MRI
  - No hippocampal volume loss to account for large temporal horns
  - Corpus callosum bowing and accentuation of aqueduct flow void are predictors of a good response to shunting in some studies.
  - Presence of periventricular deep white matter lesions indicative of small-vessel disease are associated with a poor response.
- Isotope cisternography. A tracer injected into the CSF normally fails to enter the ventricles. In patients with NPH reflux of tracer into the ventricles within 24 hours with retention for 24–48 hours. The usefulness of this technique is controversial.

Management

- There is no gold standard for diagnosis.
- Decision for shunting is based on clinical impression with supportive evidence from radiology and some of the following:
  - Timed walking test before and after removing 30 mL of CSF at LP
  - Cranial bolt monitoring over 24 hours showing 15B-waves
  - Measuring the rate of absorption of CSF by infusion of saline into the thecal sac, which represents compliance of the CSF compartments. Normal value 5–10 mmHg/mL/min. More than 18 mmHg/mL/min implies active hydrocephalus.

Complications of shunts

Shunt infection

Usually caused by coagulase-negative Staphylococcus aureus. Ninety percent present within 3 months of insertion.

Clinical features

- General malaise
- Pyrexia
- Headache, vomiting, meningism
- Abdominal tenderness or distension
- Pain and erythema around the shunt

Laboratory features

- Increased C-reactive protein
- Increased white cell count

Management

- Shunt removal
- Placement of an external ventricular drain
- Intrathecal vancomycin for 5–7 days via external ventricular drain (EVD): 5 mg if slit ventricles, 10 mg for normal ventricles, and 15 mg if dilated ventricles daily when CSF draining freely or every 3 days when drain clamped

Other complications

- Misplacement
- Hemorrhage
- Subdural hematomas can occur in the first 6 months especially in the elderly. Ten to fifteen percent may require surgery.
- Epilepsy. See DVLA regulations. May not drive for 6 months
- Shunt malfunction
  - Blockage at ventricular, distal, or valve level. Palpation of the shunt reservoir is unreliable.
  - Underdrainage: symptoms of hydrocephalus persist. Requires placement of a valve with lower pressure variety
  - Overdrainage: symptoms of low pressure, i.e., postural headache, dizziness, tinnitus. Imaging reveals slit-like ventricles, subdural fluid collections, dural thickening, and enhancement. Replace with a higher pressure valve

Follow-up of patients with shunts

- Baseline CT 6 months after insertion
- Patient and caregivers should be given instructions about symptoms of infection and blockage.
- Documentation about type of valve should be given to the patient.
- Programmable valves should be checked after MRI.

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Chapter 15

Clinical neurophysiology

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Normal values in clinical neurophysiology *430*

Neurophysiological investigations include the following:

- Electroencephalography (EEG)
  - Used in diagnosis and management of epilepsy
  - Combined with video recordings to establish diagnosis of epilepsy
  - Assessment of epilepsy before epilepsy surgery
  - Diagnosis of infective and metabolic brain disorders, e.g., CJD, herpes simplex encephalitis, hepatic encephalopathy
- Nerve conduction studies (NCS) and needle electromyography (EMG)
  - Study of sensory and motor peripheral nerve disorders, e.g., neuropathies, radiculopathies, plexopathies, dorsal root ganglionopathies, and anterior horn cell disorders
  - Neuromuscular junction disorders
  - Skeletal muscle disorders
  - Cranial nerve disorders, e.g., facial nerve, trigeminal nerve
- Evoked potentials (EPs)
  - Study sensory and motor pathways in the peripheral and central nervous systems
  - Useful in investigation of multiple sclerosis, other spinal cord and brainstem disorders, and cranial neuropathies
  - Monitoring of spinal cord function during surgery for scoliosis and of the facial nerve during acoustic neuroma surgery

The neurophysiological evaluation helps the neurologist in the following ways:

- Confirming the clinical diagnosis
- Defining type of dysfunction, e.g., axonal versus demyelinating neuropathy
- Excluding certain disorders in differential diagnosis
- Detecting subclinical disease, e.g., optic nerve demyelination or vasculitic peripheral neuropathy
- Defining severity of disease and indicating prognosis, e.g., extent of axonal degeneration in Guillain–Barré syndrome
- Monitoring change in disease over time
- Identifying muscles most suitable for injection with botulinum toxin in treating focal dystonias

Electroencephalography (EEG): introduction

Conventional EEGs are noninvasive recordings of spontaneous brain electrical activity, obtained using scalp electrodes that record rapidly changing events. EEG waveforms represent spatiotemporal averages of synchronous excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) generated by cortical pyramidal cells (layers II, III, IV).

EEG electrode placement Most widely used is the standardized "International 10/20 system," which utilizes three bony landmarks of the skull: nasion (bridge of the nose directly under the forehead), inion (bony

protuberance in the middle of the back of the head), and pre-auricular point (depression of bone in front of the external auditory meatus). Disc electrodes (metal disc or cup, with diameters of 4–10 mm) are placed on the scalp and held by an adhesive conductive paste that holds the electrode in place and serves as an electrical contact.

EEG display EEG is typically represented as a graph of voltage (vertical axis, y) versus time (horizontal axis, x). Recordings are displayed in various combinations of channels called "montages."

EEG activity The difference in electrical potential between two recording electrodes generates a wave; a wave or sequence of waves represents EEG activity. The form of the waves is typically classified based on several important characteristics, such as morphology, repetition, frequency, amplitude, field of distribution, reactivity (such as eye opening/closure, applied noxious stimuli), and persistence. The frequency of EEG activity is classified into four bands: delta (up to 4/second or 4 Hz), theta (4–8/second or 4–8 Hz), alpha (8–13/second or 8–13 Hz), and beta (>13/second or >13 Hz) frequencies. The normal waking EEG (Fig. 15.1) in an adult usually has posterior dominant bilateral alpha activity that is enhanced on eye closure. The background frequency for most young children is 6 Hz by 1 year of age, 7 Hz by 2 years of age, and 8 Hz by 3 years of age. The lower limit of the alpha frequency band is reached by 8 years of age.

EEG recording

The routine EEG recording includes the following:

- Twenty-one scalp electrodes placed according to the International 10/20 system of electrode placement
- Simultaneous single-channel ECG recording
- Two eye movement channels monitor state of alertness or eye movements during various stages of sleep (such as rapid eye movements during sleep).

EEG recordings are susceptible to artifacts (noncerebral signals in origin). These can be divided into physiological (generated by various body activities, such as muscle, movement, blinking) and nonphysiological (arising from either external electrical interference or electrical malfunctioning of the recording system). They are often technically difficult in younger children, uncooperative patients, and in ICUs (due to electrical interference with power lines and equipment). See Fig. 15.1.

Routine EEGs are usually initially recorded in the waking state. The recording room is quiet and dimly lit to allow the patient to become drowsy. Activation procedures may enhance abnormalities. These include the following:

- Hyperventilation: vigorous overbreathing for 2–5 minutes, followed by recording for at least 1 minute. This is contraindicated in patients with various heart and lung conditions, cerebrovascular diseases with poor or borderline cerebral perfusion, as well as acute cerebral disorders (recent stroke, subarachnoid hemorrhage). With adequate effort, normal responses are characterized by slow waves, usually in the theta to delta range. The slowing (delta range, high amplitude) is most

Figure 15.1 Normal waking adult EEG, longitudinal bipolar montage. ECG, electrocardiogram; Eye Mvt, eye movement channel.

pronounced in children and more prominent in persons with lower serum glucose. This is especially useful in childhood absence epilepsy, as lack of epileptiform abnormality virtually excludes the diagnosis in an untreated patient. Less often, this maneuver activates focal epileptiform patterns and focal slow waves.

- Photic stimulation: delivered by a strobe light (flashing light at variable rates) 20–30 cm from the patient's central vision. Flash frequencies between 2 and 60/second are used, including during eye closure, in a room with low illumination. Photosensitivity is manifested by generalized self-sustaining epileptiform abnormalities. The photoparoxysmal (photoepileptiform, photoconvulsive) response consists of generalized or posterior dominant spike and slow-wave (epileptiform) discharges. Generalized epileptiform activity that is independent of the photic stimulus and outlasts its termination is typically associated with increased risk of seizures. Normal photic responses consist of sharp discharges time-locked to the stimulus rate and ending with cessation of stimulation. The presence of a generalized photoparoxysmal response is strong evidence of an underlying primary generalized epilepsy (e.g., juvenile myoclonic epilepsy).
- Sleep deprivation: usually requires sleep deprivation for up to 24 hours, which may activate epileptiform activity in susceptible individuals

Long-term EEG monitoring

Prolonged simultaneous video and EEG monitoring records behavior and can capture epileptic events, contributing to the classification of seizure disorders.

- Indicated in differentiating epileptic seizures from nonepileptic events
- Essential in presurgical evaluation to help identify the anatomical site of seizure onset

May involve the following:

- Additional anterior temporal, sphenoidal (flexible wire with uninsulated tip placed near the sphenoidal wing to detect activity in the temporal lobes), or foramen ovale electrodes
- More invasive EEG recordings with subdural strip or intracerebral depth electrodes (intracranial EEG studies) to localize epileptiform activity
- Stimulation of underlying cortex via subdural electrodes in waking state by applying an electrical current to individual electrodes; used to map the location of eloquent areas (those important for speech) prior to resection
- Ambulatory 16- to 32-channel systems allowing the patient to perform daily activities while trying to capture the clinical event in question. Limitations due to artifacts and lack of simultaneous video recordings; useful in cases where spells only occur in certain circumstances

EEG: use and abuse

EEG is useful in the investigation of the following:

- Epilepsy: epileptiform abnormality on EEG is specific but not sensitive for the diagnosis of epilepsy as a cause of any paroxysmal event or transient loss of consciousness. In epileptic patients sensitivity is 25%–55% and specificity is 80%–98%.
- Impaired consciousness/coma—to rule out subclinical seizures or nonconvulsive status epilepticus
- Toxic confusional states
- Diffuse degenerative disorders, e.g., CJD, AD
- Metabolic encephalopathies, e.g., hepatic failure, uremia
- Cerebral trauma
- Parasomnias—episodes of unusual behaviors during sleep such as night terrors, sleepwalking, REM sleep behavior disorder

EEG has more limited value in the workup and diagnosis of other conditions such as multiple sclerosis, migraine headaches, mental retardation and psychoses, although abnormalities or even seizures have been described in association with all of these conditions.

EEG abnormalities that indicate definite pathology:

- Epileptiform discharges
- Generalized or focal slowing
- Absence of normal background rhythms—diffuse or focal/unilateral
- Periodic phenomena: relatively stereotyped waveforms (often sharp waves) that appear in a periodic or quasi-periodic fashion; commonly seen in diffuse encephalopathies.

Contraindications

- Should not be used to rule out nonconvulsive status in patients who are able to answer questions and follow commands
- A normal EEG does not exclude the diagnosis of epilepsy; cannot rule it out unless the event in question is recorded during the EEG

EEG: normal rhythms and benign variants

Normal rhythms

- Alpha rhythm: 8–13 Hz waves seen maximally over the bilateral posterior head regions during relaxed wakefulness and with eye closure; lower limit of this frequency should be reached by 8 years of age; attenuates with eye opening and periods of alertness
- Beta rhythm: Faster frequencies, usually in the 13–25 Hz band, maximum seen over the bi-fronto-central regions. Enhanced by drowsiness; when of higher amplitude and more widespread, diffuse distribution is secondary to medication (sedative-hypnotic) effect

- Mu rhythm: 7–12 Hz centrally located rhythm, arciform morphology, attenuated unilaterally with movement of the opposite extremity; also called "ubiquitous rhythm of the sensorimotor cortex at rest"
- Theta rhythm: 4–7 Hz activity, activated diffusely during drowsiness
- Posterior slow waves of youth: delta waves (1–3 Hz) with superimposed alpha activity, observed maximally over the posterior head regions; most common in children and adolescents, rarely in up to 20% of young adults

Benign variants

These include variations of normal rhythms and patterns with an apparent "epileptiform" morphology, which should be properly recognized and differentiated from patterns with an abnormal significance.

- Rhythmic midtemporal theta of drowsiness (psychomotor variant): bursts of rhythmic theta range waves, 5–7 Hz, often with a notched appearance, commonly seen during drowsiness and stage 2 sleep, in normal adolescents and adults
- Subclinical rhythmic electrographic discharge in adults (SREDA): rhythmic 5–7 Hz theta activity, seen bilaterally and synchronously over the parietal and posterior temporal regions, with an average duration of 40–80 seconds; primarily seen in adults over age 50 years
- Midline theta rhythm (Ciganek rhythm): rhythmic sharply contoured 4–7 Hz theta activity, occurring usually over the midline region, during wakefulness and drowsiness
- Frontal arousal rhythm (FAR): bursts of several second duration 7–10 Hz waves, maximally over the frontal head regions; disappears when patient is fully awake
- Fourteen- and 6-Hz positive bursts: short trains of arch-shaped waveforms with alternating positive spiky component and a negative rounded waveform resembling a sleep spindle; occur at a rate of either 14 Hz or 6 Hz; seen in children and adolescent age groups during drowsiness
- Small sharp spikes (benign epileptiform transients of sleep, BETS): low voltage, short duration (<50 milliseconds), single spike; no prominent subsequent slow wave typically seen in epileptiform discharges; do not occur in trains; seen in adults during drowsiness
- Six-hertz spike-and-wave bursts ("phantom spike and wave"): brief bursts of 5–7 Hz generalized spike and wave discharges seen in adolescents and young adults during wakefulness and drowsiness; the spike component is characteristically small in amplitude; FOLD variant: female, occipital region, low in amplitude, drowsiness; WHAM variant: wakefulness, higher amplitude, anterior distribution, males
- Wicket spikes: intermittent trains or clusters of arciform waveforms that resemble the Greek mu or wicket; seen predominantly in adults over 30 years of age
- Breach rhythm: high voltage, spiky appearance activity in the region of a skull defect

EEG: abnormal rhythms

Cortical rhythms are generated locally in the cerebral cortex but are modulated at both thalamic and reticular activating system (brainstem) levels. Sleep spindles are likely generated in the thalamus (reticular nucleus) and projected to the cortex. The reticular activating system is involved in the transitions between different states of arousal.

Diffuse slowing

- Most common EEG abnormality, nonspecific as to cause
- Seen in various encephalopathies, such as toxic, metabolic, anoxic, and degenerative conditions
- May be intermittent, intermittent rhythmic, continuous

Focal slowing

- Indicative of localized, parenchymal (white matter) dysfunction
- May be seen in patients with focal seizure disorders, even in the absence of an underlying structural lesion
- Focal voltage attenuation suggests gray matter dysfunction, as well as regional fluid collections (subdural, epidural)
- Persistent, nearly continuous delta waves are usually an indication of an underlying white matter structural abnormality (Fig. 15.2C), or may be seen postictally

Periodic complexes

Periodicity refers to repetitive discharges reflecting dysfunction of gray and white matter

- Periodic lateralized epileptiform discharges (PLEDS; see Fig. 15.2A): complex of spikes and slow wave discharges, at 1 to 2 Hz frequency; most commonly seen in acute cerebral infarctions (35%), infections (HSE), other mass lesions (e.g., metastases), cerebral abscess, anoxia; highly correlated with seizures. Tend to resolve after 1 or 2 weeks, even when underlying lesion is progressive
  - See "Viral meningoencephalitis," p. 297
  - May be seen bilaterally independent (BIPLEDS), most often associated with anoxic encephalopathy and central nervous system infections; poor prognosis
- Generalized periodic discharges occur in
  - Cerebral anoxia
  - Subacute sclerosing panencephalitis (SSPE): simultaneous bilateral complexes of slow and fast components, repeating at 4–10 second intervals
  - Creutzfeldt–Jakob disease (CJD; Fig. 15.2B): discharges at frequency close to 1 per second; may be confused with ECG pickup on scalp, and simultaneous ECG channel is important
  - In both SSPE and CJD: progressive loss of cortical rhythms until repetitive complexes occur on a silent background

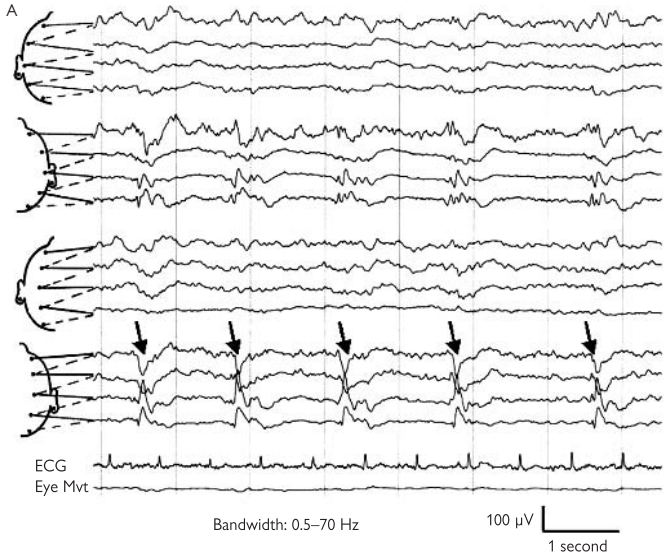

Figure 15.2 (A) Right-sided periodic lateralized epileptiform discharges (PLEDS), indicated by arrows, in an elderly drowsy patient 2 days following right-sided cerebral infarction. ECG, electrocardiogram; Eye Mvt, eye movement channel.

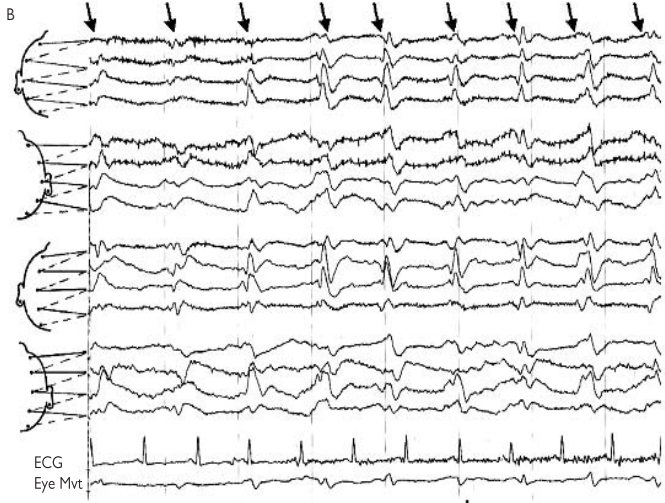

Figure 15.2 (*Contd.*) (B) Generalized periodic sharp wave complexes, indicated by arrows, in an adult patient with Creutzfeldt–Jakob disease (CJD). ECG, electrocardiogram; Eye Mvt, eye movement channel.

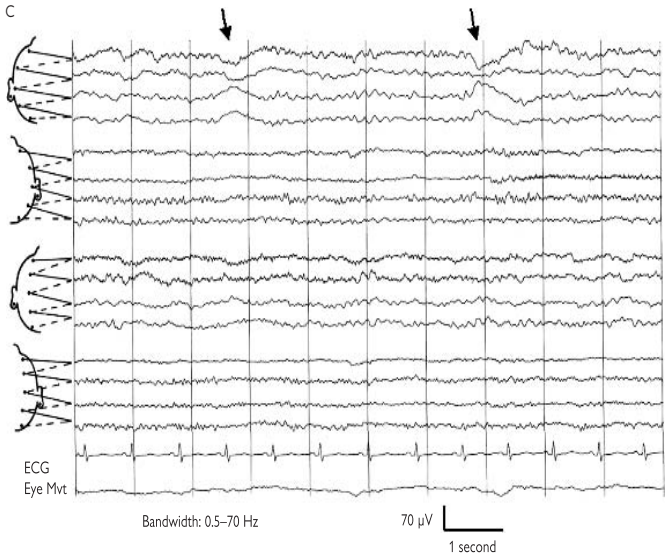

Figure 15.2 *(Contd.)* (C) Left temporal focal delta rhythms, indicated by arrows, in a waking adult patient who had had a left-sided subarachnoid hemorrhage 2 years previously. ECG, electrocardiogram; Eye Mvt, eye movement channel.

EEG and epilepsy

Epileptiform activity

The hallmarks are as follows:

- Spikes with 20–70 ms duration
- Sharp waves with 70–200 ms duration
- Spike and slow-wave activity or sharp and slow-wave activity
- Electrographic seizures, with or without clinical correlate
- However, similar patterns can occur in the normal EEG but are recognized by the characteristic waveforms, topography, and circumstances of occurrence (see "EEG-Benign Variants")

Diagnostic strategy in epilepsy

- Misinterpretation of nonepileptiform features is an important cause of false-positive EEG reports. Prevalence of rigorously defined epileptiform discharges (EDs) is 0.5%–2% in normal adults.
- A normal EEG does not exclude a diagnosis of epilepsy.
- Thirty-three percent of epileptic patients exhibit interictal epileptiform discharges in waking EEGs (Fig. 15.3A); 16% never do. The probability of interictal epileptiform abnormality in a patient with epilepsy in a 30-minute waking recording is 1 in 3.
- Repeated waking EEGs can increase detection rate of interictal epileptiform abnormalities in patients with epilepsy; EDs are recorded on the first EEG in 30%–50% of patients with epilepsy, and in 60%–90% by the third EEG.
- Sleep EEG, particularly following sleep deprivation (Fig. 15.3B), increases yield to 80%; hyperventilation and photic stimulation also increase probability of focal or generalized interictal epileptiform abnormalities.
- If interictal EEG is persistently normal, consider long-term video–EEG monitoring.
- There is no relationship between presence or absence of interictal epileptiform abnormalities on EEG and seizure frequency or response to medication.

EEG and seizure classification

- EEG findings together with patient's clinical history support distinction between focal and generalized seizures. This will guide therapy. Identification of focal elements at onset of seizures is important, as focal events can rapidly propagate to secondarily generalized discharges.
- Focal asymmetry, slowing, or generalized abnormalities may assist in differentiation.
- Photosensitivity occurs in 5% of epileptic patients, but more so in the generalized epilepsy syndromes, especially in juvenile myoclonic epilepsy. See Figure 15.3C.

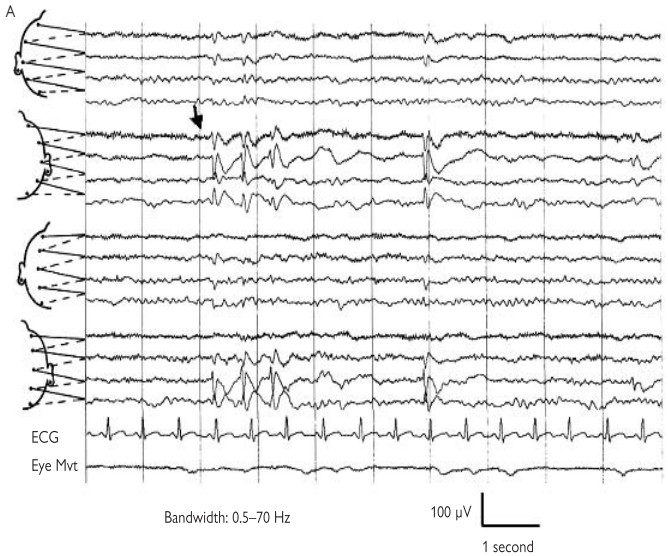

Figure 15.3 (A) A burst of focal subclinical epileptic activity, indicated by arrow, in the right centrotemporal region of a waking adult patient. ECG, electrocardiogram; Eye Mvt, eye movement channel.

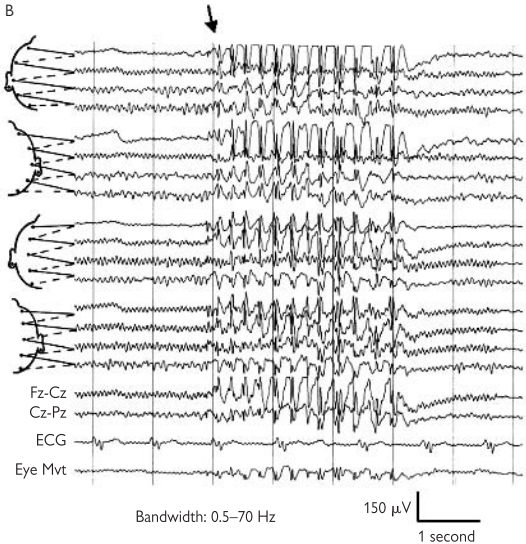

Figure 15.3 (*Contd.*) (B) A burst of generalized subclinical spike/polyspike and slow-wave activity, indicated by arrow, in a waking adult patient following sleep deprivation. A previous waking EEG had been normal. The patient had one generalized seizure. ECG, electrocardiogram; Eye Mvt, eye movement channel.

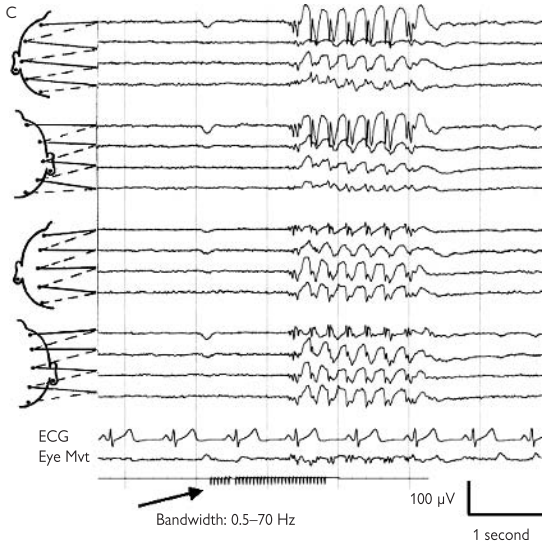

Figure 15.3 (*Contd.*) (C) A burst of generalized subclinical spike/polyspike and slow-wave activity in a waking adult patient elicited by photic stimulation. The arrow indicates the photic stimulation markers. ECG, electrocardiogram; Eye Mvt, eye movement channel

EEG and discontinuation of treatment

In children and adults EEG can be a useful guide, as persistent epileptiform abnormalities indicate a high risk of relapse if discontinuation of treatment is under consideration. In certain benign epilepsy syndromes and benign generalized epilepsy syndromes, EEG may still be abnormal, but treatment can be discontinued. By the same token, patients may have a normal EEG, but it can be too risky to discontinue treatment.

EEG and diffuse cerebral dysfunction

EEGs can be helpful in patients with altered mental status, ranging from mild memory difficulties to coma. The results, however, are nonspecific as to etiology. EEG is useful in the following clinical situations:

- Detection of seizure activity in a comatose patient
- Suggesting etiology in undiagnosed coma
  - May reveal focal abnormalities from intracerebral space-occupying lesions
  - Periodic lateralized epileptiform discharges (PLEDS) over the temporal region can suggest herpes simplex encephalitis
- Diagnosing diffuse degenerative conditions, e.g., CJD, SSPE
- Help in identification of psychogenic coma or the locked-in syndrome
- Prognostic guide after anoxic brain injury
- Evaluation of brain death

EEG patterns in diffuse cerebral dysfunction

Generalized slowing (Fig. 15.4)

- Can suggest toxic or metabolic encephalopathy
- Sensory activation using visual, auditory, tactile, or painful stimuli is important, as reactive EEG activity implies a better prognosis.

Periodic spiking occurs in post-anoxic encephalopathy and is associated with a poor prognosis.

Alpha coma Nonreactive 8–12/second activity is associated with a poor prognosis.

Burst suppression

- Bursts of high-amplitude slow and sharp activity alternating with periods of attenuation of background EEG activity
- May occur after severe anoxic brain injury, general anesthesia, hypothermia, and barbiturate overdose
- Used as a marker of adequate barbiturate dosage in status epilepticus treatment

Triphasic waves. Can occur in the following:

- Metabolic conditions: hepatic, uremic, and anoxic encephalopathy
- CJD
- Postictal state

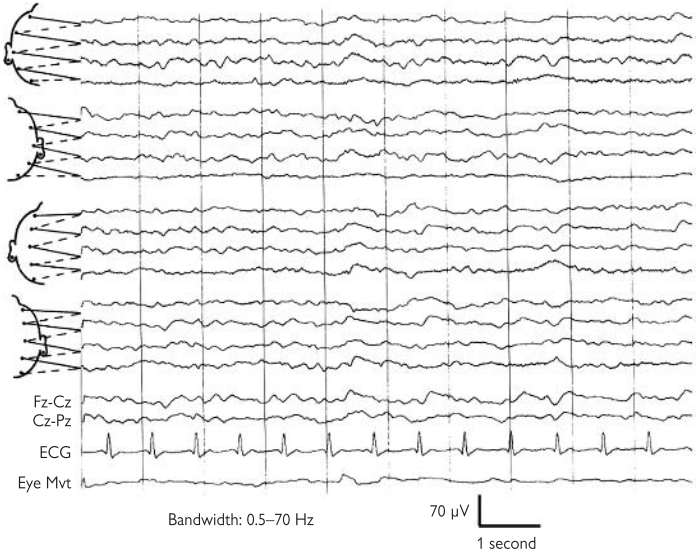

Figure 15.4 Diffuse symmetrical theta and delta slowing in a waking adult with Lewy body dementia. ECG, electrocardiogram; Eye Mvt, eye movement channel.

Periodic complexes
- Periodic lateralized epileptiform discharges (PLEDS) occur in destructive lesions: ischemic stroke, intracerebral hemorrhage, encephalitis
- Generalized or asymmetrical periodic sharp waves often found in sporadic CJD at some stage of the illness; do not occur in variant CJD or familial CJD
- Generalized periodic stereotypic complexes occur in SSPE and correlate with myoclonic jerking

Epileptiform patterns
- Nonconvulsive status epilepticus
- Postictal

Normal EEG
- Locked-in syndrome with lesion in pontine tegmentum
- Psychogenic unresponsiveness

Electrical inactivity
- Absence of brain waves >2 μV amplitude

In brain death, severe poisoning, general anesthesia, hypothermia.

EEG and drug effects

Numerous drugs can affect EEG activity, often in particular patterns.

Slowing of alpha at therapeutic doses
- Phenothiazines
- Opiates
- Phenytoin
- Carbamazepine
- Valproate
- Steroids

Spikes at therapeutic doses
- Tricyclics (rare)
- Monoamine oxidase inhibitors (MAOIs) (rare)
- Enflurane

Increased beta at therapeutic doses
- Tricyclics
- MAOIs
- Benzodiazepines
- Barbiturates
- Chloral hydrate

- Meprobamate
- Amphetamines
- Cocaine
- Psilocybin
- Diphenhydramine

Focal slowing at therapeutic doses

- Lithium

Periodic complexes similar to Creutzfeldt-Jakob disease (CJD)

- Lithium

Triphasic waves at toxic levels

- Lithium

Sharp waves at toxic doses

- Lithium
- Penicillin
- Isoniazid

Attenuates or eliminates photoparoxysmal response in generalized epilepsy

- Valproate

Alpha coma at toxic doses

- Benzodiazepines
- Barbiturates
- Chloral hydrate
- Meprobamate
- Meperidine

Spindle coma at toxic doses

- Alcohol
- Imipramine

EEG in the intensive care unit

Clinical neurological assessment is limited in the unconscious or paralyzed and ventilated patient. EEG can provide important information about cerebral function, particularly in detecting potentially remediable disorders. EEG is sensitive to ischemia and hypoxia (pyramidal neurons in cortical layers 3 and 5 are both responsible for EEG activity generation and vulnerable to hypoxia and ischemia). EEG abnormalities need to be distinguished from the effects of sedatives and anesthetic agents.

Continuous EEG monitoring is used:

- To detect seizures in patients with status epilepticus or nonconvulsive seizures who are paralyzed and ventilated; without continuous EEG monitoring, diagnosis and treatment of nonconvulsive seizures and status epilepticus may be delayed
- To assist management of sedation and increased ICP in patients following acute severe head trauma; if increased ICP cannot be controlled with conventional measures, high-dose barbiturate has been proven to be effective in lowering it; continuous EEG monitoring is the only reliable guide to monitoring barbiturate dosing, which is typically titrated to burst-suppression pattern on EEG
- In assessment and early identification of hemispheric infarctions; CT scans often can be normal or equivocal in acute stroke; however, EEG changes occur within minutes of onset of ischemia, which has important diagnostic and therapeutic implications
- In the diagnosis and prognosis of coma (Fig. 15.5) changes in reactivity, variability, and wake–sleep state in the EEG may provide clues to the etiology of coma.
  - Focal repetitive periodic lateralized epileptiform discharges (PLEDS) are typically seen in herpes simplex encephalitis.
  - Diffuse slow waves occur in metabolic encephalopathy, anoxic brain injury, drug overdose
  - Spindle or beta coma patterns can be seen in overdoses with tricyclic agents, benzodiazepines, barbiturates
  - Alpha coma is typically seen in patients with severe anoxic encephalopathy and is characterized by a diffusely distributed alpha activity, nonreactive to external stimuli

Prognosis after cardiac arrest

- Recovery of continuous activity within first 4 hours correlates with good prognosis. In contrast, recovery at 48 hours indicates poor prognosis.
- Isoelectric and burst suppression patterns not caused by drugs or hypothermia indicate a poor prognosis as well.

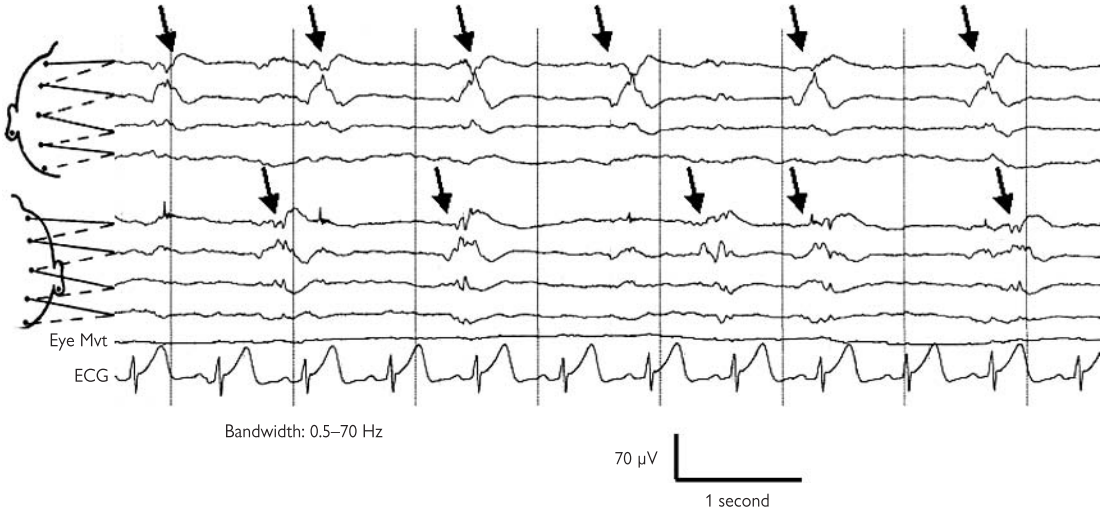

Figure 15.5 Loss of normal background rhythms and bilateral independent periodic lateralized epileptiform discharges (PLEDS), indicated by arrows, in an adult comatose patient following hypoglycemia. ECG, electrocardiogram; Eye Mvt, eye movement channel.

Technical summary of nerve conduction studies (NCS)

Standard NCS assess function of the large myelinated motor and sensory fibers.

- NCS depend on many technical factors
  - Subject's age, gender, and height
  - Skin temperature: must be controlled or a correction applied; conduction velocity varies by 2.4 m/s/1 degree from 29°C to 38°C
  - Recording equipment
  - Operator experience
- NCS are either
  - *Orthodromic* where direction of propagated potentials is the same as normal physiological conduction in the nerve, e.g., sensory nerve distal-to-proximal
  - *Antidromic* where studies are in the opposite direction to normal physiological conduction, e.g., sensory nerve proximal-to-distal
- Conduction velocity (CV) reflects the velocity of the fastest conducting nerve fibers.
- Durations of the sensory nerve action potential (SNAP) or compound muscle action potential (CMAP) waveforms reveal the spectrum of CV in large nerves (Fig. 15.6).
- Motor conduction velocity (MCV) in meters/second is calculated by: distance (millimeters) between two separate points of stimulation, one close to muscle being recorded, the other more proximal ÷ difference between onset latencies of the proximally elicited and distally elicited CMAP waveforms elicited by separate supramaximal stimulation (milliseconds).
- Compound muscle action potentials (CMAPs) are recorded from the skin overlying a muscle in response to stimulation of the motor nerve to that muscle. Onset latency, amplitude, area, and duration are measured.
- Sensory nerve action potentials (SNAPs) are recorded from a nerve in response to supramaximal stimulation of the nerve at another site. Onset latency, peak latency, amplitude, area, and duration are measured.
- Sensory conduction velocity (SCV) is calculated: distance (millimeters) between stimulation and recording electrodes ÷ onset latency of the SNAP waveform (milliseconds).
- F wave. Supramaximal distal stimulation of a motor nerve also elicits an impulse that travels antidromically to the axon hillock region of the spinal cord where it elicits further motor fibers that propagate back to the muscle. Only explores 1%–3% of motor axons in a nerve
  - Gives information on conduction over the whole length of motor nerve, including proximal sections
  - Parameters noted are frequency of occurrence out of 20 stimuli, minimum latency and range of latencies.
- H reflex
  - Measures conduction through afferent and efferent fibers in a monosynaptic reflex arc

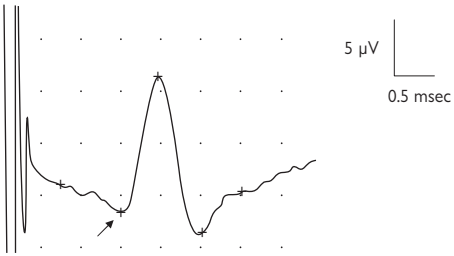

Figure 15.6 Sensory nerve action potential. The ulnar sensory fibers were stimulated at digit V using surface electrodes and the recording electrodes were placed over the ulnar nerve at the wrist. Arrow indicates first positive peak, used in this example to calculate sensory conduction velocity (in this case, 57 meters/sec). The amplitude (14 μv) was measured between the negative (upward) peak and the second positive (downward) peak. Ten waveforms were averaged. Supramaximal stimulation rate = 1/sec. Illustration has been redrawn for clarity.

  - Usually recorded from calf muscles in response to submaximal stimulation of Ia afferents in the tibial nerve at the knee
  - Equivalent to eliciting ankle deep tendon reflex
  - Most helpful in assessing for S1 radiculopathy
  - Absent if F wave and other NCS are abnormal
- Blink reflex

Assesses integrity of trigeminal and facial nerves and their direct and indirect connections in the pons and medulla

Evaluation of proximal nerve conduction

Indirect studies

- F wave
- H reflex

Direct studies

- Nerve root stimulation by
  - High-voltage surface electrical stimulation
  - Monopolar needle electrode stimulation
  - Magnetic stimulation

Special studies

Repetitive nerve stimulation (RNS)

- Slow RNS: 4–10 impulses at rate of 3/sec: assesses neuromuscular junction
  - Decremental response with nadir at fourth impulse seen characteristically in myasthenia gravis, botulism; may also be seen in Lambert-Eaton myasthenic syndrome (LEMS) and some congenital myasthenic syndromes as well as in reinnervating muscle.
- Fast RNS: 1 second of stimulation at rate of 20–50 pulses/sec
  - Incremental response seen LEMS and botulism; most pronounced in LEMS

Peripheral nerve disorders: NCS abnormalities

NCS will help classify a peripheral nerve disorder into the following categories:

- Sensorimotor
- Pure sensory or pure motor
- Axonal, demyelinating, or mixed
- Generalized, multifocal, or length dependent

Demyelinating neuropathies

Characterized by decreased conduction velocities with preserved SNAP and CMAP amplitudes.

- Abnormalities supportive of demyelinating neuropathy include
  - Dec CV: <70%–80% of lower limit of normal
  - Increased F wave latencies: >130% upper limit of normal
  - Increased distal sensory and motor latencies: >130% upper limit of normal
  - Decreased CMAP amplitude from proximal stimulation compared to distal stimulation (motor conduction block): 20%–50% decrease required depending on distance from stimulation to recording electrode (smaller percent decrease with shorter distance)
- In many hereditary demyelinating neuropathies, abnormalities tend to be diffuse and to a similar degree in all nerves.
- In acquired demyelinating neuropathies
  - Focal slowing
  - Temporal dispersion (increased duration of action potentials)
  - Regions of conduction block
- Needle EMG studies can show abnormalities indicating secondary denervation and reinnervation, depending on severity and chronicity.

Axonal neuropathies

Characterized by:

- Decreased or unrecordable SNAPs and CMAPs
- With severe axonal loss, conduction velocity may be reduced as result of loss of fastest conducting fibers
- Needle EMG confirms axonal degeneration
  - Spontaneous activity (positive sharp waves and fibrillations) in a quiet muscle denotes denervation and can suggest acuity of insult.
  - Examination of voluntary motor units with needle examination may reveal characteristic features of denervation and reinnervation.

Focal neuropathies (See Fig. 15.7.)

- Lesions may cause focal regions of demyelination. Stimulation of the nerve distal to lesion elicits a normal response. Proximal stimulation produces a response with delayed latency corresponding to localized conduction slowing, e.g., ulnar neuropathy at the elbow. Inching studies (in which stimulating electrode is moved in 1 cm increments away from or toward the recording electrode) and comparative studies may localize precise site of demyelination (Fig. 15.7)

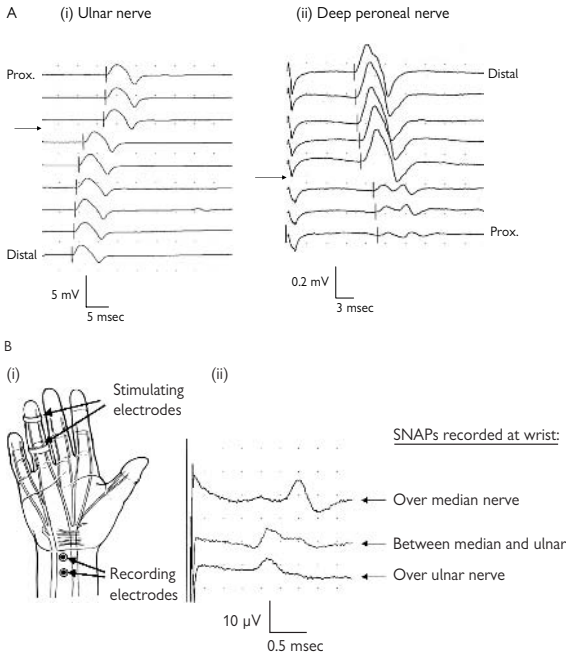

Figure 15.7 (A) Localization of focal neuropathies. (i) Inching studies, recording from abductor digiti minimi muscle, demonstrating ulnar motor slowing (arrow) localized to the region of the medial epicondyle. Supramaximal stimuli over the nerve at 2-cm intervals, proximal to distal. (ii) Inching studies, recording from extensor digitorum brevis muscle, demonstrating deep peroneal motor slowing and partial motor conduction block (arrow) localized to the region of the head of fibula. Supramaximal stimuli over the nerve at 2-cm intervals, distal to proximal. (B) Carpal tunnel syndrome. (i) The position of the stimulating surface electrodes on digit IV and the active recording electrodes at the wrist. (ii) The median sensory nerve action potential (SNAP) occurring significantly later than the ulnar SNAP, demonstrating slowed sensory conduction velocity of median fibers from digit IV compared to ulnar fibers from digit IV. (Active stimulating-to-recording electrode distances equal for the three active recording electrode positions.)

- Focal lesion may result in conduction block at the site of the lesion. For example, with neurapraxia of the common peroneal nerve at the fibular head resulting in foot-drop, distal response may be normal but proximal stimulation may not elicit a response due to conduction block.
- Focal lesion may also cause axonal degeneration distal to site of lesion. This can result in reduced amplitude of SNAPs and CMAPs.

Technical summary of needle electromyography (EMG)

Needle EMG involves extracellular recording of muscle action potentials using either monopolar or concentric needle electrodes. In typical clinical practice, needle EMG is a qualitative assessment and therefore operator dependent.

- A motor unit refers to the a single anterior horn cell body, its axon, terminal axon branches, and all subsequently innervated muscle fibers (10–2000 muscle fibers per anterior horn cell, depending on the muscle type).
- A motor unit action potential (MUAP) is the summation of activity from all of the muscle fibers of one motor unit.
- Transection of a motor nerve is followed by regrowth at 1 mm/day.

Technical aspects

- Concentric needle electrode (CNE) is inserted into the belly of the muscle at rest
- Insertional activity is assessed. No electrical activity should be seen in a normal muscle at rest other than that generated by needle insertion.
  - An exception to this rule occurs when the needle touches or is in close proximity to a motor end plate. In that event, a characteristic "sea shore" sound may be heard and irregular small spikes or even positive sharp waves may be seen.
- Subject is asked to activate muscle voluntarily. MUAPs are studied and reflect synchronous discharge of all muscle fibers in a motor unit.
- With minimal effort, a few motor units fire initially at 5–7/sec. With more effort, more motor units of higher amplitude and faster firing frequencies are recruited.
- During minimal effort, individual MUAPs are assessed for morphology, including amplitude, phases and duration (see Fig. 15.8).
- Recruitment and interference pattern of MUAPs are assessed at increasing levels of contraction and at maximal voluntary effort.

Special studies

Single-fiber EMG (SFEMG) utilizes a special needle with two apertures to record two or more muscle fibers of the same motor unit firing nearly synchronously.

- Measures synchrony of activation (jitter) and detects failure of a muscle fiber to fire (blocking) within a motor unit
- Sensitive for detecting neuromuscular junction defects
- Also "positive" in floridly active denervation
- Allows estimation of fiber density in cases of denervation

Notes

- Needle EMG may be contraindicated in patients with coagulopathies, e.g., oral anticoagulant medication, hemophilia, thrombocytopenia. Discuss with clinical neurophysiologist.
- Transient bacteremia may occur, causing endocarditis in those with prosthetic or diseased valves. Discuss with clinical neurophysiologist.

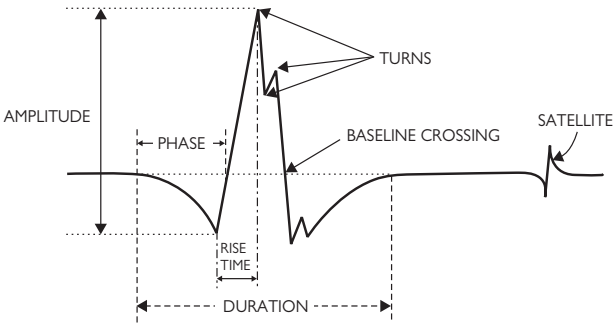

Figure 15.8 Schema of motor unit action potential with characteristics that can be measured. (From Daube JR [2002]. *Clinical Neurophysiology*, 2nd ed., Oxford, England: Oxford University Press. By permission of Oxford University Press.)

- Muscle biopsy findings in a muscle examined by needle EMG can yield misleading information due to muscle trauma and localized inflammation.
- Serum creatine kinase (CK) levels may rise by 150% of normal after needle EMG. Returns to normal after 48 hours

Normal needle EMG

Spontaneous activity at rest

End plate noise (see Fig. 15.9)

- Multiple small negative monophasic potentials—associated with sound of "sea shore"
- Reflect miniature endplate potentials (MEPPs)—the spontaneous "leakage" of quanta of acetylcholine from the presynaptic membrane at the motor endplate, which results in depolarizations at the postsynaptic membrane that do not reach a level to propagate an action potential

End plate spikes (see Fig. 15.9)

- Irregular biphasic negative potentials of low amplitude representing depolarization of a single muscle fiber—attributed to the needle touching terminal axon twigs

Insertional activity (see Fig. 15.10)

- Essentially injury potentials caused by damage to muscle membranes by needle. Normal insertional activity lasts less than 300 milliseconds after a needle movement.

Voluntary MUAPs

Triphasic potentials (see Fig. 15.11)

- Smallest motor units recruited first
- Firing is semirhythmic, starting at 5–7/sec. Second motor unit is recruited when firing rate of first is approximately 10/sec.

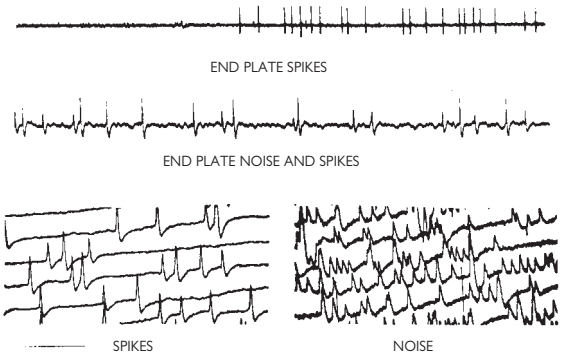

Figure 15.9 Spike form of normal spontaneous activity in the end plate region. End plate noise is seen as an irregularity in the baseline at a low amplification in addition to the spike form. (From Daube JR [2002]. *Clinical Neurophysiology*, 2nd ed., Oxford, England: Oxford University Press. By permission of Oxford University Press.)

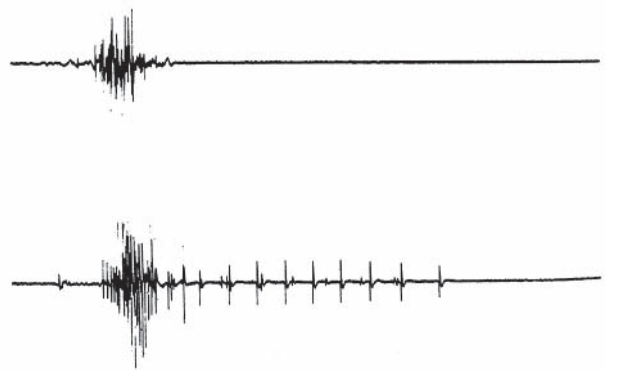

Figure 15.10 (Top) Normal short burst of insertional activity with needle movement. (Bottom) Increased insertional activity with a train of repetitive firing potentials after the insertional burst. (From Daube JR [2002]. *Clinical Neurophysiology*, 2nd ed., Oxford, England: Oxford University Press. By permission of Oxford University Press.)

Figure 15.11 Typical normal recruitment pattern of voluntary motor units. Smallest motor units recruited first followed by larger motor units for gradation of power.

- Recruitment ratio <5 (frequency of firing of fastest-firing motor unit divided by total number of motor units firing). Values >5 support motor neuron loss.
- Type I fibers (oxidative) recruited first; Type II fibers (glycolytic) recruited last

Needle EMG: patterns of abnormality

Spontaneous activity at rest

Fibrillations and positive sharp waves (see Fig. 15.12).

- Generated by individual muscle fibers
- Reflect increased excitability of muscle membranes due to alteration in resting membrane potentials
- Occur in
  - Recent denervation
  - Myopathic processes
  - Chemodenervation, e.g., botulism

Fasciculation potentials

- Result from irregular spontaneous discharges of a group of muscle fibers from all or part of a motor unit
- May result from pathology in the anterior horn cell, motor root, or more distal motor nerve
- May also be a benign condition exacerbated by fatigue and stimulants

Myotonia (see Fig. 15.13)

- Characterized by rhythmic discharges of muscle fibers occurring spontaneously or triggered by insertion of EMG needle into muscle. Waveforms resemble positive sharp waves or fibrillations. Discharges wax and wane in amplitude, producing a noise resembling a decelerating motorcycle.

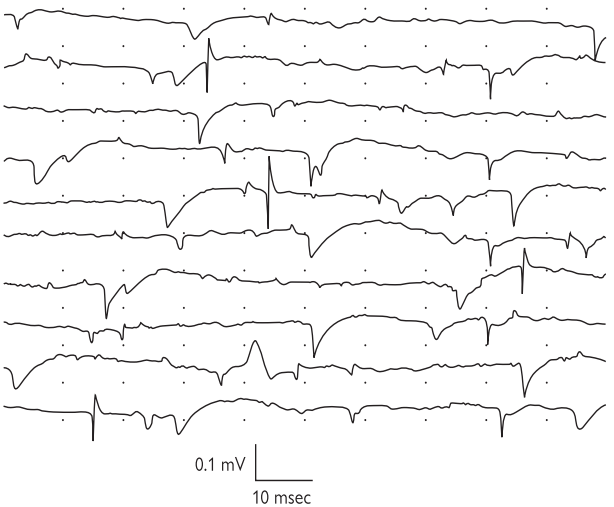

Figure 15.12 Concentric needle EMG recording of fibrillations and positive sharp waves (downgoing) at rest indicating recent denervation of the muscle. Illustration has been redrawn for clarity.

- Occurs in
  - Myotonia congenita
  - Myotonic dystrophy
  - Paramyotonia congenita
  - Hyperkalemic periodic paralysis
- Electromyographic, as opposed to clinical myotonia, is also seen in
  - Polymyositis
  - Hypothyroidism
  - Acid maltase deficiency, typically in the paraspinal muscles

Complex repetitive discharges (see Fig. 15.13)

- Have a uniform shape, frequency, and amplitude. Have an abrupt onset, mimicking the sound of a machine gun, with a frequency of 5–100/sec
- Represent a group of muscle fibers firing in near synchrony through fiber-to-fiber ephaptic transmission ("circus rhythm": depolarization of one muscle fiber causes the depolarization of adjacent fiber)
- Denotes chronic disease: pathological correlate is a group of atrophic fibers
- Occur in
  - Myopathies, e.g., polymyositis, Duchenne muscular dystrophy

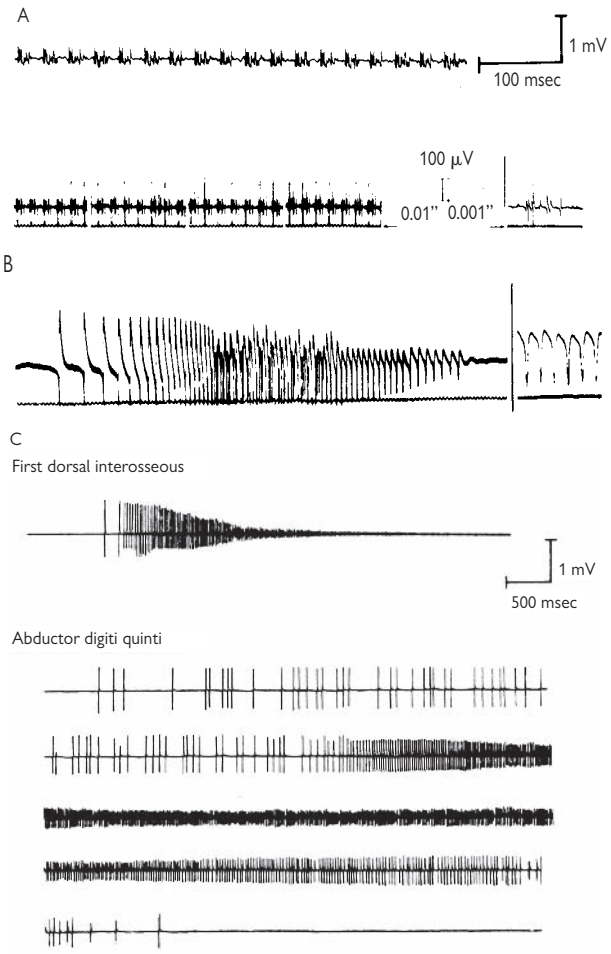

Figure 15.13 Abnormal spontaneous activity. (A) Complex repetitive discharge: a group of muscle fibers firing repetitively in near synchrony—sound of a motorboat; (B) Myotonic discharge: muscle fiber membrane instability results in waxing and waning positive discharges of 40–100 Hz frequency—sound of a motorcycle revving. (C) Neuromyotonia: high-frequency waning discharges firing at > 200/sec—sound of a dive bomber airplane.

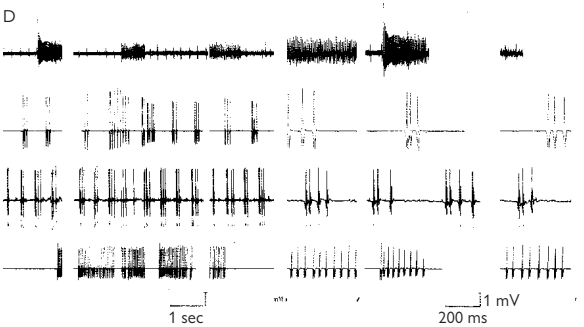

Figure 15.13 (*Contd.*) (D) Myokymia: grouped firing of motor units—sound of marching soldiers. (From Daube JR [2002]. *Clinical Neurophysiology*, 2nd ed., Oxford, England: Oxford University Press. By permission of Oxford University Press.)

- Chronic denervation, e.g., radiculopathy, spinal muscular atrophy, hereditary neuropathies
- Myxedema

Neuromyotonia (see Fig. 15.13)

- Characterized by spontaneous and continuous rhythmical discharges at high frequencies (150–300/sec)
- Represents single fiber or motor unit discharges that originate from a distal motor axon
- Occurs in conditions associated with continuous muscle fiber activity, e.g., stiff person syndrome, encephalomyelitis with rigidity, Isaac (autoimmune) syndrome, anticholinesterase poisoning, chronic spinal muscular atrophy, intraoperative nerve irritation

Myokymia (see Fig. 15.13)

- Consists of repetitive discharges of one or more motor units, usually in complex bursts
- Occurs in chronic neuropathies and represents a nonspecific response to injury
- Occurs in radiation plexopathies
- Can be recorded in facial muscles in patients with multiple sclerosis or pontine glioma
- May be exacerbated by hyperventilation-induced hypocalcemia

Neurogenic processes (affecting motor axons)

- Denervation results in fewer motor units that can be activated voluntarily. Remaining viable motor units may reinnervate those muscle fibers that have lost their prior axonal connections.

- Acute denervation changes recorded from a muscle at rest initially include spontaneous fibrillations and positive sharp waves as the muscle membrane loses stability.
- Reinnervation results in denser motor units that contain increased numbers of fibers manifesting as long-duration high-amplitude MUAPs. Motor unit fiber density is increased; grouping of fibers of similar type occurs. Newly reinnervated MUAPs are unstable (Fig. 15.14), reflected in their changing morphology on needle examination.

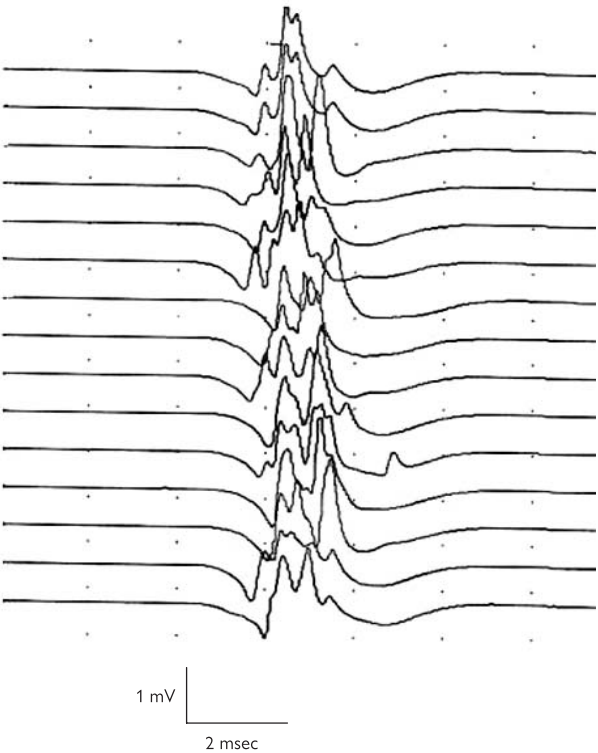

Figure 15.14 Concentric needle EMG recording, in Raster display, of a triggered unstable and irregular motor unit potential, indicating recent reinnervation.

Myopathic processes

- Excessively full interference pattern so that baseline is obliterated at earlier effort than in normal muscle
- Low-amplitude and short-duration MUAPs
- Complex or polyphasic MUAPs due to increased variation in diameter of pathological muscle fibers
- Fibrillations and positive sharp waves at rest in inflammatory and some hereditary myopathies
- Unstable MUAPs indicate a recent or active process.
- Stable late satellite potentials may be present in longstanding myopathic disorders.

NCS and needle EMG findings in neuropathies

Axonal loss

NCS:

- Absent or low-amplitude sensory and/or motor responses
- Conduction velocities preserved (normal or in cases of severe axonal loss >80% lower limit of normal)

Needle EMG:

- Acute: normal or decreased recruitment
- Subacute: decreased recruitment, increasing duration, amplitude and polyphasia of MUAPs
- Chronic: high-amplitude, long-duration motor units with decreased recruitment (recruitment ratio >5). With ongoing denervation, polyphasic MUAPs are still seen.

Demyelination

- Hereditary
  - *NCS:* prolonged latencies, slow conduction velocities, prolonged F waves, no focal conduction block (except in hereditary neuropathy with pressure palsies [HNPP]), a hereditary dysmyelination syndrome in which compact structure of myelin is disrupted as a result of duplication of PMP gene on chromosome 22; conduction block is seen clinically at sites usually unassociated with compression injuries
  - *Needle EMG*: can be normal; however, secondary axonal loss over years leads to chronic pattern of denervation (represented by large-amplitude, long-duration motor units with decreased recruitment in distal limb muscles)

- Acquired (focal or generalized): Guillain-Barre syndrome is the prototypical acquired demyelinating syndrome (see Box 15.1)
  - *NCS:* prolonged latencies, slow conduction velocities, prolonged F waves as seen in hereditary demyelinating neuropathies. However, the pathognomic hallmark is presence of conduction block and temporal dispersion.
  - *Needle EMG:* normal +/– decreased recruitment in weak muscles whose nerves are affected by conduction block. In chronic demyelinating disorders, secondary axonal loss may occur resulting in neurogenic MUAPs (see EMG in "Axonal loss" earlier).

Box 15.1 Guillain–Barré syndrome

- Prototypical acquired demyelinating syndrome
- Motor nerves usually more involved than sensory nerves
- Autonomic nerve involvement may be prominent and life-threatening (labile blood pressure and cardiac arrythmias)

Early NCS

- Studies may be normal
- Prolonged distal motor latencies
- Reduced recruitment and prolonged F waves
- Early prolongation of F waves represents proximal conduction block.

Late NCS

- Widespread slowing in sensory and motor nerves
- Temporal dispersion of SNAP or CMAP
- Conduction block detected by decreased CMAP amplitude with more proximal stimulation

Needle EMG

- Evidence of denervation in paraspinal and limb muscles 2–3 weeks after onset indicates secondary motor axonal loss as a result of primary demyelination.
- The degree of decreased CMAP amplitude and denervation on needle EMG indicates severity and guides prognosis.

GBS subgroups

- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
- Acute motor axonal neuropathy (AMAN)
- Acute motor and sensory axonal neuropathy (AMSAM)
- Miller Fisher syndrome: areflexia, ataxia, and ophthalmoplegia

NCS and needle EMG findings in plexopathies

The delineation of a plexopathy often requires an extensive electrophysiological study. Detailed knowledge of the brachial plexus in particular is necessary to localize a lesion within the plexus. The combination of abnormalities on sensory and motor NCS and on needle EMG point to localization.

NCS

- Sensory NCS: may be abnormal and, if so, have localizing value
- Motor NCS—abnormalities narrow the possibilities of affected root, trunk, or cord

Needle EMG

- Denervation +/– reinnervation seen in affected muscles

NCS and needle EMG findings in radiculopathies

NCS

- Normal SNAPs, as pathology is proximal to the dorsal root ganglion.
- H-reflex from flexor carpi radialis or soleus muscles may be delayed or absent in C7 or S1 radiculopathies, respectively.

Needle EMG

- Denervation of paraspinal muscles helps to differentiate root lesions from more peripheral nerve lesions.
- Evidence of denervation is required in ≥2 muscles innervated by each motor root.
- Needle EMG of adjacent myotomes determines extent of involvement.

NCS and needle EMG findings in motor neuron disease (MND)

MND can be difficult to diagnose in the early stages, especially in bulbar onset cases or if confined to one limb. The electrophysiological examination can support a clinical diagnosis of MND but is not itself diagnostic.

NCS

- Sensory NCS normal
- Motor NCS with decreased amplitude of CMAPs and normal conduction velocities (axonal loss pattern)

Needle EMG

- Active denervation with partial reinnervation involving different roots and nerves corresponding to different spinal and bulbar segments (Table 15.1)

Table 15.1 ALS: Revised El Escorial Criteria 2006

Clinically definite ALS	UMN and LMN signs in 3 of 4 body regions
Clinically probable ALS	UMN and LMN signs in 2 body regions with some UMN signs rostral to UMN signs
Clinically possible ALS	UMN and LMN signs in 1 body region OR UMN signs only in 2 body regions OR LMN signs rostral to UMN signs

Note: Four body regions are bulbar, cervical, thoracic, and lumbosacral.

Note

- Progression of disease can be monitored by serial studies and repeated measurement of CMAPs.
- It is of vital importance to search for motor conduction block such as may be seen in a treatable mimic of MND: multifocal motor neuropathy (MMN)

NCS and needle EMG findings in myopathies

NCS

- Normal nerve conduction velocities
- Normal sensory nerve action potential amplitudes
- CMAP amplitudes of motor nerves may be reduced in *severe* myopathy involving distal muscles.

Needle EMG

- Abnormalities may be patchy.
- Needle EMG cannot differentiate between different types of myopathy.
- Spontaneous activity at rest, which may be confined to paraspinal muscles or may be widespread, indicates inflammatory myopathies or some metabolic myopathies.
  - Fibrillations
  - Positive sharp waves
  - Complex repetitive discharges
- Myopathic motor unit potentials (MUPs) reflecting loss of muscle fibers and increased fiber type variation (Fig. 15.15)
  - Polyphasic
  - Low amplitude
  - Short duration

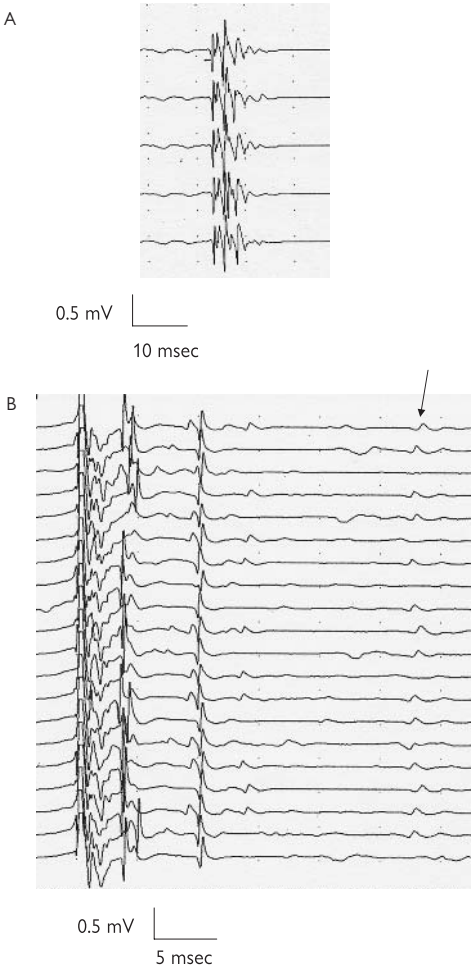

Figure 15.15 Concentric needle EMG recording, myopathic patterns. (A) Raster display of a triggered low-amplitude polyphasic stable motor unit potential. (B) Raster display of a triggered polyphasic motor until potential, associated with late (satellite) potentials (see arrow).

NCS and needle EMG findings in neuromuscular transmission disorders

Classified by abnormality within neuromuscular junction
- Postsynaptic, e.g., myasthenia gravis
- Presynaptic, e.g., Lambert–Eaton myasthenic syndrome, botulism

Note: it is important to study clinically affected muscles.

Myasthenia gravis

NCS
- Normal sensory nerve conduction studies
- Amplitude of CMAP from affected muscle may be decreased due to motor endplate destruction with normal motor conduction velocities.

Needle EMG
- No evidence of denervation or reinnervation (except in severest cases)

*Repetitive nerve stimulation (RNS) (*see Fig. 15.16)
- Slow rate of repetitive supramaximal stimulation (3/sec) results in "decrement": i.e., >10% decreased amplitude of fourth CMAP compared to first CMAP
- Maximal voluntary contraction of the muscle for 20 seconds or a train of high-rate stimulation (20–50/sec) may result in some increase in CMAP amplitude (repair of decrement), but <200%: i.e., post-activation potentiation due to transient increase in acetylcholine release.
- Degree of decrement correlates with clinical severity

Single-fiber EMG (SFEMG) (see Fig. 15.17)
- Studies transmission in individual motor endplates
- Performed if RNS is negative and clinical suspicion for neuromuscular junction defect remains high
- Reveals subclinical neuromuscular transmission defects
- Increased jitter found in extensor digitorum communis muscle in all cases of moderate or severe generalized MG and 96% of mild cases. In ocular MG, increased jitter of frontalis muscle found in 89%

Lambert–Eaton myasthenic syndrome (LEMS)

NCS
- Sensory nerve conduction studies are usually normal unless associated with a paraneoplastic neuropathy.
- CMAP amplitudes are absent or decreased if rested muscle is tested.
- Normal motor conduction velocities

RNS (see Fig. 15.16)
- Slow rate of repetitive supramaximal stimulation (3/second) elicits a decrement >10%, similar to MG above
- Maximal voluntary contraction for 20 seconds or high rate of RNS (20–50/sec) results in >200% of CMAP post-activation potentiation due to transient increased release of acetycholine. See Fig. 15.18.

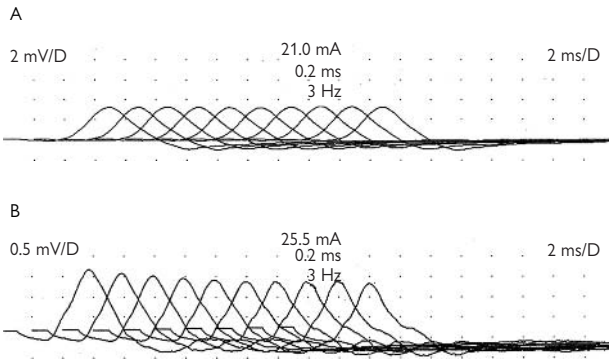

Figure 15.16 Repetitive nerve stimulation at 3 Hz, recorded from nasalis muscle. (A) Normal (2 mV/D); (B) 15% decrement in a myasthenic patient (0.5mV/D).

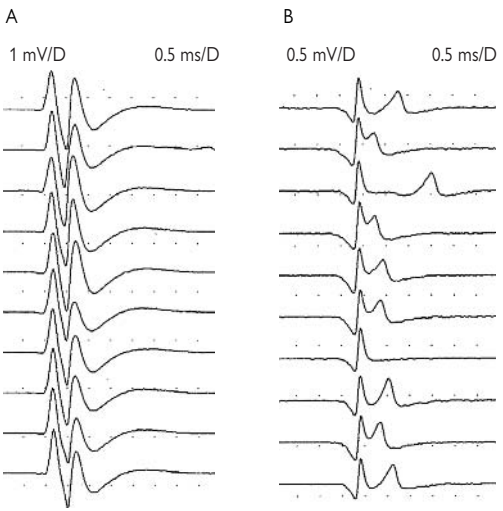

Figure 15.17 [CN.12 (AAL)] Single-fiber EMG. (A) Normal jitter; (B) increased jitter and blocking in a myasthenic patient.

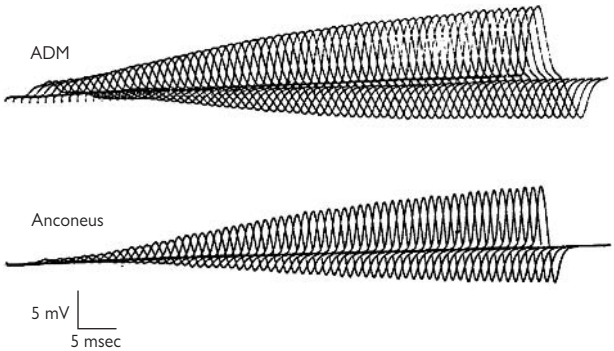

Figure 15.18 Increment in a patient with Lambert–Eaton myasthenic syndrome (LEMS). Repetitive nerve stimulation at 20 Hz, recorded from abductor digiti minimi (ADM) and anconeus muscles.

Needle EMG

- No evidence of denervation or reinnervation on needle EMG

SFEMG

- Increased jitter in clinically affected muscles

Botulism

NCS

- Sensory nerve conduction studies normal
- Motor nerve conduction studies reveal low amplitudes and normal conduction velocities

RNS

- Slow rate of repetitive supramaximal stimulation (3/sec) elicits a decrement >10%, similar to MG above
- Maximal voluntary contraction for 20 seconds or high rate of RNS (20–50/sec) results in CMAP post-activation potentiation due to transient increased release of acetylcholine.

Needle EMG

- Spontaneous activity as in denervation seen on needle EMG (muscle fibers are denervated chemically)

SFEMG

- Increased jitter in clinically affected muscles

Quantification of small-fiber neuropathy

Pain and temperature perception

Painful neuropathies may develop without clear abnormalities on nerve conduction studies or EMG. This is due to the involvement of small nerve fibers dispersed diffusely in the skin. Patients often complain of burning or stinging pain or electrical shocks. The most common cause of small-fiber neuropathy is impaired glucose handling, though a number of autoimmune and hereditary disorders are also associated with it, e.g., Sjogren disease, amyloidosis. Often the diagnosis is made on a clinical basis without electrophysiological testing. In cases where confirmation is desired, the following testing may be done:

- Skin biopsy to assess intraepidermal nerve fiber density
- Quantitative sensory testing (QST)
  - Assesses threshold of heat and cold perception (small-fiber function)
  - Assesses threshold of vibratory perception (large-fiber function)

Autonomic function

Autonomic nerve dysfunction represents a type of small-fiber neuropathy. Autonomic fibers are small in caliber, unmyelinated, and diffusely dispersed. A number of specialized electrophysiological tests have been developed to assess small-fiber autonomic function, many of which are only available in specialized academic centers.

Routine cardiac autonomic testing might include the following:

- Tilt table testing
- Heart rate or blood pressure response to deep breathing
- Heart rate or blood pressure response to Valsalva maneuver
- Heart rate or blood pressure response to standing from the recumbent position

More specialized testing might include the following:

- PET scan or more commonly SPECT scan with MIBG to elucidate cardiac autonomic neuropathy (CAN)
- Thermoregulatory sweat testing (TST): assesses sweating response to a warm environment
- Quantitative sudomotor axon reflex testing (QSART): measures sympathetic skin response (sweat production) to direct application of acetylcholine

Evoked potentials (EPs)

Introduction

In contrast with EEG, which is a reflection of spontaneous electrical activity of the brain, evoked potentials (EPs) are generated by applied external stimuli to sensory systems (visual, auditory, or somatosensory evoked potentials) or motor pathways (motor evoked potentials). EPs

consist of complex of waveforms with positive and negative components. Abnormalities of EPs include the following:

- Absence of the wave
- Increased wave latency
- Decreased wave amplitude

Clinical applications

- Demyelinating disorders
- Identify and localize abnormal sensory system function as an objective measure in conjunction with the neurological examination
- Prognosis: abnormalities of the somatosensory evoked potentials in the setting of hypoxic-ischemic encephalopathy

Visual evoked potentials (VEPs)

VEPs are recorded from the scalp and are averaged from the EEG background of the occipital cortex. The visual stimulus is a checkerboard pattern of black and white squares that reverses (white squares change to black and the black squares to white) one to three times per second. VEPs reflect integrity of the central visual field from retina, optic nerve, and cortex and are exquisitely sensitive to disorders of the optic nerves and optic chiasm.

- The full-field VEP is elicited by stimulating each eye while the subject fixates on the stimulus.
- Hemifield stimulation is helpful in assessment of postchiasmatic lesions.
- Pattern reversal electroretinography (ERG) can be recorded simultaneously with VEPs; this enables retinal abnormalities to be excluded as a cause of abnormal VEPs.

The P100, the major measurement and the most consistent waveform, is a large positive deflection that occurs at approximately 100 milliseconds after the visual stimulus and is maximal in the occipital midline.

- Latency is the most consistent parameter.
- Amplitude varies among normal individuals.
- Elicited by the following:
  - Luminance change, i.e., flash VEP
  - Contrast change with repeated reversal of the checkerboard pattern (pattern reversal VEP; Fig. 15.19A)

Applications

Most commonly used for detection of asymptomatic lesions in MS (Fig. 15.19B).

- Ninety percent of patients with a history of optic neuritis have abnormal pattern-reversal VEPs; latency of the P100 response almost always remains abnormally delayed, even if vision returns to normal.
- Seventy percent of patients with definite multiple sclerosis and no history of optic neuritis have prolonged P100 latency.
- Unilateral delay suggests impaired conduction in the visual pathway anterior to optic chiasm, since fibers arising from the nasal portion of each retina decussate at the optic chiasm.

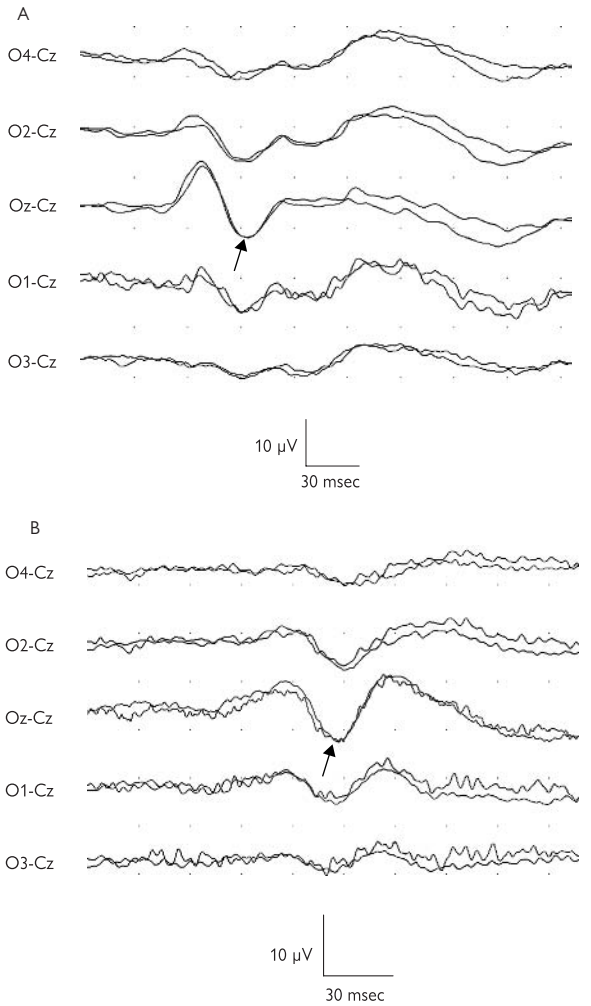

Figure 15.19 (A) Normal pattern-reversal visual evoked responses (VERs) recorded from a 25-year-old man. The midline P100 latency (indicated by arrow) was 100 msec. (B) Delayed pattern-reversal VERs recorded from a 48-year-old man with multiple sclerosis. The P100 latency indicated by arrow was 143 ms. (Visual acuity was 6/9.)

- Site of abnormality cannot be localized when delay is bilateral and equivalent from each eye (inter-eye P100 latency <6–8 msec).
- Unilateral hemispheric lesions do not alter the latency of the P100 response, given the normal response from the contralateral hemisphere.
- Possible to have recordable VEPs with cortical blindness (when an island of striate cortex is spared in extensive parieto-occipital lesions)
- VEP delays have been described with a variety of other acute and chronic diseases that affect the visual system: ocular diseases (e.g., glaucoma, retinopathies), compressive and noncompressive lesions of the optic nerve (extrinsic tumors, ischemic optic neuritis), diffuse nervous system diseases (adrenoleukodystrophies, spinocerebellar ataxias).
- Hysteria and malingering: a normal P100 latency makes lesions of the optic nerve or anterior chiasm very unlikely as cause of subjective visual loss.

Somatosensory evoked potentials (SSEPs)

SSEPs are time-locked responses following electric stimulation of afferent peripheral nerve fibers from upper (median nerve) and lower (posterior tibial nerve) limbs. They enable study of the integrity of the large-fiber sensory pathways in peripheral nerves, spinal cord (dorsal column-meniscal system), and brain.

Upper-limb SSEPs

- Stimulation of median nerve at wrist (Fig. 15.20A)
- Recordings from
  - Erb's point
  - Upper cervical cord
  - Scalp over hand area of contralateral somatosensory cortex
- Nomenclature
  - EP waveforms are named according to their polarity (N-negative, by convention upward deflection in SSEPs; P-positive)
- Generators
  - EP (N9)—Erb's point potential—afferent volley passing through the brachial plexus
  - N13—postsynaptic activity in the dorsal gray matter of the cervical cord
  - P14—activity in the caudal medial lemniscus, prior to decussation
  - N18—postsynaptic potentials from multiple brainstem structures
  - N20—activity from the contralateral primary cortical somatosensory receiving area

Lower-limb SSEPs

- Stimulation of tibial nerve at ankle (Fig. 15.20B)
- Recordings from the following:
  - PF—popliteal fossa
  - T12/L1

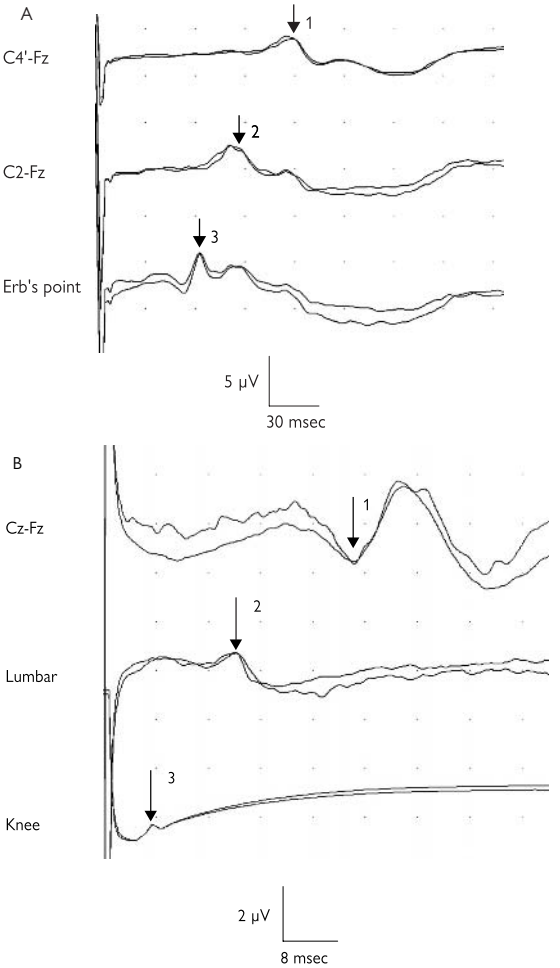

Figure 15.20 (A) Normal upper limb somatosensory evoked potentials (ULSSEPs), elicited by stimulation of the left median nerve of a 34-year-old woman at the wrist: standing height, 173 cm. Arrow 1 = cortical (N20) waveform; Arrow 2 = cervicomedullary (N13) waveform; Arrow 3 = brachial plexus potential. (B) Normal lower-limb somatosensory evoked potentials (LLSSEPs), elicited by stimulation of the left tibial nerve of a 36-year-old woman at the ankle: standing height, 180 cm. Arrow 1 = cortical (P37) waveform; Arrow 2 = lumbar (N22) waveform; Arrow 3 = peripheral nerve waveform recorded at the popliteal fossa.

  - Scalp over foot/leg area of contralateral somatosensory cortex in midline
- Generators
  - PF—spinal roots, gracile tract
  - N22—dorsal gray matter, at the lower thoracic/upper lumbar spine level
  - P31—activity in the caudal medial lemniscus
  - N34—equivalent of N18 component of the median nerve SEP, multiple brainstem structures
  - P37—cortical component, contralateral primary somatosensory area

Notes

- Lesions alter SSEPs by delaying or abolishing component waveforms. Waveform amplitude is less reliable than latency.
- Lower-limb SSEP latencies are proportional to standing height.
- Differentiate between central and peripheral causes of large-fiber sensory dysfunction
- Study proximal peripheral nerves when standard sensory NCS are normal.
- Altered by focal (strokes, syringomyelia) or diffuse (multiple sclerosis, hereditary system degenerations) processes
- Large-amplitude SSEPs, reflecting enhanced cortical excitability, are seen in progressive myoclonic epilepsy, late-infantile ceroid lipofuscinosis.
- Confirmation of nonorganic peripheral sensory loss
- Used to monitor spinal cord integrity during surgical procedures associated with potential risk of injury

SSEPs in specific conditions

Multiple sclerosis

- SSEP abnormalities present in up to 90% of patients with definite MS and 50%–60% of MS patients without sensory symptoms or signs.
- Usually associated with prolongation of central sensory latencies
- May indicate second asymptomatic lesion
- When peripheral sensory conduction is normal, it is possible to localize a lesion:
  - Above cervico–medullary junction
  - At region of cervico–medullary junction/upper cervical cord
  - Below upper cervical region but above cauda equina

Coma

- Bilateral absence of the thalamo-cortical (N18–N20) waveforms indicates poor prognosis.
- Prognostic classification based on SSEPs has been developed for posthypoxic coma.

Brain death

- The role of neurophysiological investigations in brainstem death remains controversial.
- Absent N20–P22 waveforms
- P/N13 waveform complex is preserved in 70% of brain-dead patients.

Cortical myoclonus Back-averaging techniques show abnormally large cortical waveforms in progressive myoclonic epilepsy, CJD, and posthypoxic myoclonus.

Brainstem auditory evoked potentials (BAEPs)

BAEPs (Fig. 15.21) are elicited by "clicks" presented to the ear by a headphone and generated by the auditory nerve and the brainstem. Waveforms are recorded between disc electrodes placed on the scalp at vertex and mastoid of the ear being studied. The generated signals occur within 7 milliseconds after the stimulus. Normally 6 or 7 negative waveforms are recorded. Latencies for waveforms I, III, and V are the most consistent and important in clinical practice.

- Wave I. Generated in the peripheral portion of the auditory nerve near cochlea
- Wave II. Generated in the ipsilateral dorsal and ventral cochlear nuclei
- Wave III. Generated in the superior olivary nucleus
- Wave IV. Generated in the lateral lemniscus
- Wave V. Generated in the inferior colliculus, i.e., upper pons/lower midbrain
- In approximately one-third of cases, waves IV and V are fused into a single wave/complex.
- Wave VI/VII. Generated in subcortical structures, such as the medial geniculate and the auditory radiations
- Most sensitive measure is the wave I–wave III interwave latency difference

Indications/clinical correlation

- Identifying hearing impairment in infancy or in patients who have difficulty cooperating with conventional audiography
- Determining nature of hearing loss
- Helping diagnose acoustic neuroma: 98% with acoustic neuroma have abnormal BAEPs; 33% have unrecordable BAEPs. Abnormalities include prolongation of the I to III interpeak interval, preservation of wave I with loss of the subsequent components, or loss of all waveforms (in up to 33% of cases)

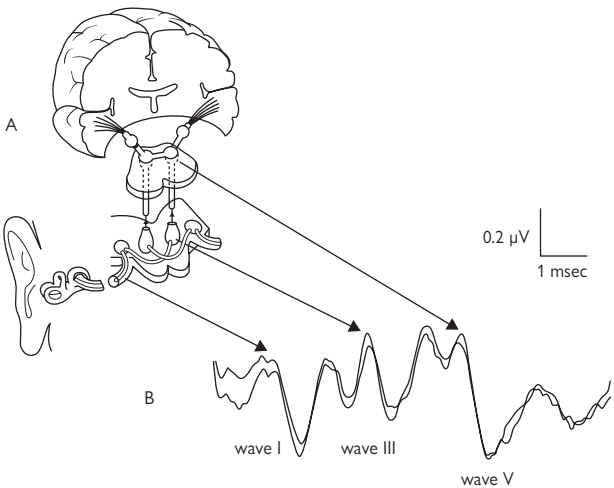

Figure 15.21 Brainstem auditory evoked responses (BAERs). (A) Schematic diagram of the auditory pathways and the origin of the BAER waveforms. (B) Example of normal BAER waveforms elicited by click stimulation to one ear of a 36-year-old woman.

- Aiding diagnosis of multiple sclerosis: abnormal in 20%–50% of patients who have no brainstem symptoms or signs; abnormal in up to 33% of patients with confirmed diagnosis; most common abnormality is decreased amplitude or absence of waves IV and V (>80% of cases); increase in the I–V interpeak latency, absence of wave III, or no response at all are other types of abnormalities.
- Aiding localization of brainstem pathology: delayed or absent wave V with normal wave III indicates abnormal conduction in the auditory pathways in the region of the pons
- Given their resistance to systemic metabolic abnormalities or medications, BAEPs are useful for demonstrating brainstem integrity in toxic and metabolic disturbances that alter EEG.
- Are usually normal in patients comatose as a result of a toxic or metabolic etiology or with a diffuse cortical process that does not affect the brainstem

Note: BAEPs are normal in cortical deafness.

Normal values in clinical neurophysiology

- Nerve conduction and evoked potential data are influenced by many subject variables, including age, height, skin temperature, and sex. Normal values that approximate most lab standards are presented in Tables 15.2, 15.3, and 15.4 as a point of reference.
- They can also be affected by technical factors such as electrode specifications, stimulating and recording parameters, recording equipment, and the person carrying out the study.
- Specific factors exist for particular studies, such as the importance of visual acuity, check size, and luminance for pattern-reversal VEPs and hearing threshold for BAEPs.

Table 15.2 Motor nerve conduction studies (surface electrodes)

	Median nerve	Tibial nerve
Muscle recorded from	Abductor pollicis brevis	Abductor hallucis brevis
Distal motor onset latency (msec)	≤4.0	≤6.2
Amplitude (mV)	≥5.0	≥5.5
Conduction velocity (m/sec)	≥50 (elbow–wrist)	≥40 (knee–ankle)
F-wave latency (msec)*		
Minimum of 20	≤30	≤58
Interside difference	≤2.5	≤3.5
H reflex minimum latency (cms)		≤33

*It is particularly important to take subject's height into account.

Table 15.3 Sensory nerve conduction studies (surface electrodes)

	Median nerve	Sural nerve
Conduction velocity (m/sec)	≥50 (digit II–wrist)	≥40 (calf–ankle)
Amplitude (μV)	≥10	≥6

Table 15.4 Evoked potential latencies

Median SSEPs	ERB's point	N13	N20	N13–N20	
Normal range (msec)	≤11	≤16	≤21	≤7	
Tibial SSEPs	N22	P37	N22–P37		
Normal range (msec)*	≤22	≤40	≤20.5		
Pattern-reversal VEP	P100	Intereye difference			
Normal range (ms)	≤115	≤6–8			
BAER	Wave I	Wave III	Wave V	Wave I–III	Wave III–V
Normal range (ms)	≤2.2	≤4.5	≤6.5	≤2.5	≤2.4

*It is particularly important to take subject's height into account.

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Neurological disability scales

Mini-Mental Status Examination (MMSE)*

I. ORIENTATION (Ask the following questions)

What is the year, season, date, day, month?

- Year, date, day, and month must be exact to receive +1 for each response.
- Correct responses for season are as follows: Spring or winter if test administered 1 day before or 1 day after official day of spring (March 20), summer or spring if test administered 1 day before or 1 day after official day of summer (June 20), fall (autumn) or summer if test is administered 1 day before or 1 day after the official day of fall (September 22), and winter or fall if test administered 1 day before or 1 day after official day of winter (December 23).
- Maximum score = 5.

Where are we? (state/county/city/clinic/floor)

- State, city, and floor must be exact to receive +1 for each response.
- County receives +1 if patient correctly identifies the county he/she is from.
- Maximum score = 5

II. IMMEDIATE RECALL

- Ask the patient if you may test his/her memory. Then **say three simple one-syllable words** without obvious associations clearly and slowly, about 1 second each. After you have said all three, **ask him/her to repeat them**.
- The first repetition determines his/her score (0–3), but keep saying them until he/she can repeat all three, up to six tries. If he/she does not eventually learn all three, recall cannot be meaningfully tested
- Maximum score = 3

III. ATTENTION AND CALCULATION

Ask the patient to begin with 100 and count backward by 7.

- Stop after patient has done 5 subtractions (93, 86, 79, 72, 65). Score the total number of correct answers
- If the patient will not attempt "the count backward test" task, ask him/her to spell the word "world" backward. The score is the number of letters in correct order (e.g., dlrow = 5, dlorw = 3)
- Maximum score = 5
- "World" backward test is not an alternative to the Calculations test. Patient must attempt Calculations test.
- Maximum score = 5.

* Folstein et al. (1975). Mini mental state. *J Psych Res* **12**:196–198.

IV. RECALL

Ask the patient to recall the three words you previously asked him/her to remember.

- Examiner is not permitted to use clues or any prompting. Score as 0 if all three words never learned in section II
- Maximum score = 3

V. LANGUAGE

NAMING

Show the patient a wrist watch and ask him/her what it is. Repeat for pencil.

- Patient must say "watch" or "pencil" to receive full credit.
- Maximum score = 2

REPETITION

Ask the patient to repeat, "No ifs, ands, or buts."

- No partial credit is given. Patient must repeat the statement exactly as it is written on this form to receive credit (e.g., "No if, ands or buts" receives no credit).
- Maximum score = 1

3-STAGE COMMAND

Before giving the patient a piece of plain blank paper say, "Take the paper in your right hand, fold it in half, and put it on the floor."

- Then hold the piece of paper out in front of the patient to grab and initiate commands.
- Do not repeat or break up commands.
- If the patient asks what he/she should do with the piece of paper, say "Do what you think I told you to do."
- Maximum score = 3

READING (maximum score = 1)

On a blank piece of paper print the sentence "Close your eyes" in letters large enough for the subject to see clearly. Ask him/her to read it and do what it says.

- Score correct only if he/she actually closes his/her eyes.
- Maximum score = 1

WRITING

Give the patient a blank piece of paper and ask him/her to write a sentence.

- The sentence is to be written spontaneously.
- The sentence must contain a subject and a verb and be sensible.
- Correct grammar, spelling, and punctuation are not necessary.
- Maximum score = 1

COPYING

On a clean piece of paper, draw intersecting pentagons, each side about 1 inch, and ask the patient to copy it exactly as it is.

- All 10 angles must be present and only two angles can be intersecting to receive one point.
- Tremor and rotation are ignored.
- Extraneous lines are permissible if all angles with two intersecting are present.
- Maximum score = 1

DERIVING TOTAL SCORE

Sum the number of correct replies to the test items. **The maximum score for this test is 30.**

Normal: 27–30**
Mild dementia: 20–26
Moderate dementia: 10–19
Severe dementia: <10

The Mini-Mental State Examination is copyright protected. Kits for testing, alternative questions in special circumstances, normative data for age and education, and software may be purchased through the Psychological Assessment Resources, Inc, website: http://www.minimental.com/

Clinical Dementia Rating Scale

The Clinical Dementia Rating Scale attaches a numerical value to describe the symptoms of dementia through a structured interview subjectively assessing 6 domains. A composite score is generated which is descriptive of level of dementia: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), or 3 (severe).

Memory

0 = no memory loss or slight inconsistent forgetfulness
0.5 = consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness
1 = moderate memory loss; more marked for recent events; defect interferes with everyday activity
2 = severe memory loss, only highly learned material retained: new material lost rapidly
3 = severe memory loss: only fragments remain

** Score may be adjusted for age and level of education.

Orientation
- 0 = fully oriented
- 0.5 = fully oriented but with slight difficulty with time relationships
- 1 = moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere
- 2 = severe difficulty with time relationships; usually disoriented to time, often to place
- 3 = oriented to person only

Judgment and problem solving
- 0 = solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance
- 0.5 = slight impairment in solving problems, similarities and differences
- 1 = moderate difficulty in handling problems, similarities and differences; social judgment usually maintained
- 2 = severely impaired in handling problems, similarities and differences; social judgment usually impaired
- 3 = unable to make judgments or solve problems

Community Affairs
- 0 = Independent function as usual in job, shopping, volunteer and social groups
- 0.5 = slight impairment in these activities
- 1 = unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection
- 2 = no pretense of independent function at home; appears well enough to be taken to function outside the family home
- 3 = appears too ill to be taken to functions outside the family home

Home and Hobbies
- 0 = life at home, hobbies, and intellectual interests well maintained
- 0.5 = life at home, hobbies, and intellectual interests slightly impaired
- 1 = mild but definite impairment of functions at home; more difficult chores and complicated hobbies and interests abandoned
- 2 = only simple chores preserved; very restricted interests, poorly maintained
- 3 = no significant function in the home

Personal care
- 0 = fully capable of self care
- 1 = needs prompting
- 2 = requires assistance in dressing, hygiene, and keeping of personal effects
- 3 = requires much help with personal care; frequent incontinence

Morris JC (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 43:2412–2414.

Positive and Negative Syndrome Scale (PANSS)

Appropriate for: Patients with schizophrenia **Administered by:** Personnel trained in psychiatric interview techniques, with experience working with populations with schizophrenia (e.g., psychiatrists, mental health-care professionals) **Time to complete:** 30–40 minutes

PANNS summary

PANSS* is a 30-item rating instrument evaluating the presence/absence and severity of positive, negative, and general psychopathology of schizophrenia. The scale was developed from the BPRS and the Psychopathology Rating Scale. All 30 items are rated on a 7-point scale (1=absent; 7=extreme).

PANSS scale benefits

- Broad evaluation—PANSS covers positive and negative symptoms associated with schizophrenia, as well as other symptoms (e.g., aggression, thought disturbance, depression)
- Provision of clinical descriptors for each item improve reliability
- Training packages are available
- Reliable history—A widely recognized and utilized assessment tool, particularly in clinical studies
- Test/re-test—Features a test/re-test function to evaluate reliability of ratings
- Factor structure is well established
- BPRS rating scale can be derived from PANSS (validity open to question)
- PANSS is an advance on BPRS, addressing broader psychopathology and greater reliability

PANSS scale challenges

- Comprehensive tool—PANSS includes 30 items, necessitating a long interview with the patient (30–40 minutes). In busy clinical practice, the duration of patient interviews is insufficient to allow administration of PANSS. In patients with cognitive dysfunction symptoms, responses may become less accurate toward the end of the interview.
- Less history than BPRS
- Patient subjectiveness—Items are assessed based on patient perceptions relating to their experiences in the previous week; patients' views might be influenced by experience of previous interviews and results might be subjectively influenced.

For further information, including details of how to obtain this scale, please contact customer service of Multi-Health Systems at http://www.customerservice@mhs.com

The variable results of positive-negative research with schizophrenics underscore the importance of well-characterized, standardized measurement techniques. We report on the development and initial standardization

*Kay SR, Fiszbein A, Opler LA. (1987). The positive and negative syndrome scale for schizophrenia. *Schizophr Bull* **13**:261–276.

of the PANSS for typological and dimensional assessment. Based on two established psychiatric rating systems, the 30-item PANSS was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology. It thus constitutes four scales measuring positive and negative syndromes, their differential, and general severity of illness. Study of 101 schizophrenics found the four scales to be normally distributed and supported their reliability and stability. Positive and negative scores were inversely correlated once their common association with general psychopathology was extracted, suggesting that they represent mutually exclusive constructs. Review of five studies involving the PANSS provided evidence of its criterion-related validity with antecedent, genealogical, and concurrent measures, its predictive validity, its drug sensitivity, and its utility for both typological and dimensional assessment.

Unified Parkinson's Disease Rating Scale*

I. MENTATION, BEHAVIOR AND MOOD

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

III. MOTOR EXAMINATION

18. Speech
    0 = Normal.
    1 = Slight loss of expression, diction, and/or volume.
    2 = Monotone, slurred but understandable; moderately impaired.
    3 = Marked impairment, difficult to understand.
    4 = Unintelligible.

19. Facial expression
    0 = Normal.
    1 = Minimal hypomimia, could be normal "poker face".
    2 = Slight but definitely abnormal diminution of facial expression.
    3 = Moderate hypomimia; lips parted some of the time.
    4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more. (head, upper and lower extremities)

20. Tremor at rest
    0 = Absent.
    1 = Slight and infrequently present.
    2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
    3 = Moderate in amplitude and present most of the time.
    4 = Marked in amplitude and present most of the time.

* Fahn S, Elton RL, and members of the UPDRS Development Committee (1987). The Unified Parkinson's Disease Rating Scale. In Fahn S, Marden SD, Cdne DB, Goldstein M (Eds.) *Recent Developments in Parkinson's Disease*, Vol. 2. Florham Park, NJ: Macmillan Healthcare, pp. 153–163.

21. Action or postural tremor of hands
    0 = Absent.
    1 = Slight; present with action.
    2 = Moderate in amplitude, present with action.
    3 = Moderate in amplitude with posture holding as well as action.
    4 = Marked in amplitude; interferes with feeding.
    (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

22. Rigidity
    0 = Absent.
    1 = Slight or detectable only when activated by mirror or other movements.
    2 = Mild to moderate.
    3 = Marked, but full range of motion easily achieved.
    4 = Severe, range of motion achieved with difficulty.
    (Patient taps thumb with index finger in rapid succession.)

23. Finger taps
    0 = Normal.
    1 = Mild slowing and/or reduction in amplitude.
    2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4 = Can barely perform the task.
    (Patient opens and closes hands in rapid succession.)

24. Hand movements
    0 = Normal.
    1 = Mild slowing and/or reduction in amplitude.
    2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4 = Can barely perform the task.
    (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

25. Rapid alternating movements of hands
    0 = Normal.
    1 = Mild slowing and/or reduction in amplitude.
    2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4 = Can barely perform the task.
    (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

26. Leg agility
    0 = Normal.
    1 = Mild slowing and/or reduction in amplitude.
    2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
    3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
    4 = Can barely perform the task.
    (Patient attempts to rise from a straight-backed chair, with arms folded across chest.)

27. Arising from chair
    0 = Normal.
    1 = Slow; or may need more than one attempt.
    2 = Pushes self up from arms of seat.
    3 = Tends to fall back and may have to try more than one time, but can get up without help.
    4 = Unable to arise without help.

28. Posture
    0 = Normal erect.
    1 = Not quite erect, slightly stooped posture; could be normal for older person.
    2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
    3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
    4 = Marked flexion with extreme abnormality of posture.

29. Gait
    0 = Normal.
    1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
    2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
    3 = Severe disturbance of gait, requiring assistance.
    4 = Cannot walk at all, even with assistance.
    (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

30. Postural stability
    0 = Normal.
    1 = Retropulsion, but recovers unaided.
    2 = Absence of postural response; would fall if not caught by examiner.
    3 = Very unstable, tends to lose balance spontaneously.
    4 = Unable to stand without assistance.

31. Body bradykinesia and hypokinesia
(Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement, which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (in the past week)

V. MODIFIED HOEHN AND YAHR STAGING (see Table A1.4)

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

Glasgow Coma Scale

The Glasgow Coma scale provides an assessment of depth and duration of coma and impaired consciousness. A patient's best responses: eye opening, motor response, and verbal response are scored and summated.

Eye opening
1 = None, even with application of painful stimuli
2 = Eyes open to painful stimulus
3 = Eyes open to verbal stimulus (not necessarily to command)
4 = Eyes open spontaneously

Motor Response
1 = None, even with application of painful stimuli
2 = Extensor posturing (decerebrate) at baseline or in response to pain
3 = Flexion in response to pain (decorticate posturing)
4 = Withdrawal response to pain
5 = Localization to pain
6 = Follows commands

Verbal Response
1 = None
2 = Incomprehensible speech (e.g., moan/groan)
3 = Inappropriate: intelligible words or phrases produced; no conversational exchange
4 = Confused: attempts made to respond to questions
5 = Oriented to self, time, location, and situation

Points are totaled to arrive at a number signifying degree of brain injury/dysfunction:
3–8: severe
9–12: moderate
13–15: mild

Reference: Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *The Lancet* 1974; 7872:81–4.

Table A1.1 National Institutes of Health Stroke Scale (NIHSS)

Instructions	Scale Definition
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct—there is no partial credit for being close.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the nonparetic hand. Substitute another one step command if the hands cannot be used.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done.	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (including cortical blindness).
4. Facial Palsy: Ask, or use pantomime to encourage—the patient to show teeth, raise eyebrows, and close eyes.	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).

Table A1.1 (*Contd.*)

Instructions	Scale Definition
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation.	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. Untestable (UN) = Amputation or joint fusion. 5a. Left Arm _____ 5b. Right Arm_____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation.	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion. 6a. Left Leg _____ 6b. Right Leg_____
7. Limb Ataxia: Test with eyes open. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion.
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss.	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.

Instructions	Scale Definition
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological examination.	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list.	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier.
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

*Note that this is an abbreviated version of the instructions for the NIHSS and is provided for reference purposes. For further information, please see the full version of the scale which is publicly available courtesy of the National Institutes of Neurological Disorders and Stroke (NINDS) at http://www.ninds.nih.gov/doctors/stroke_scale_training.htm

(A)

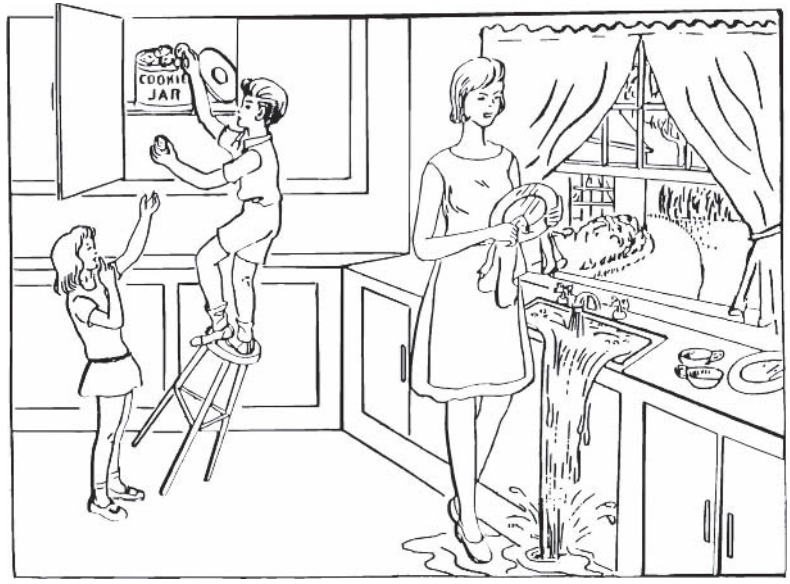

Figure A.1 (A) Picture for NIHSS language testing (provided by NINDS).

(B)

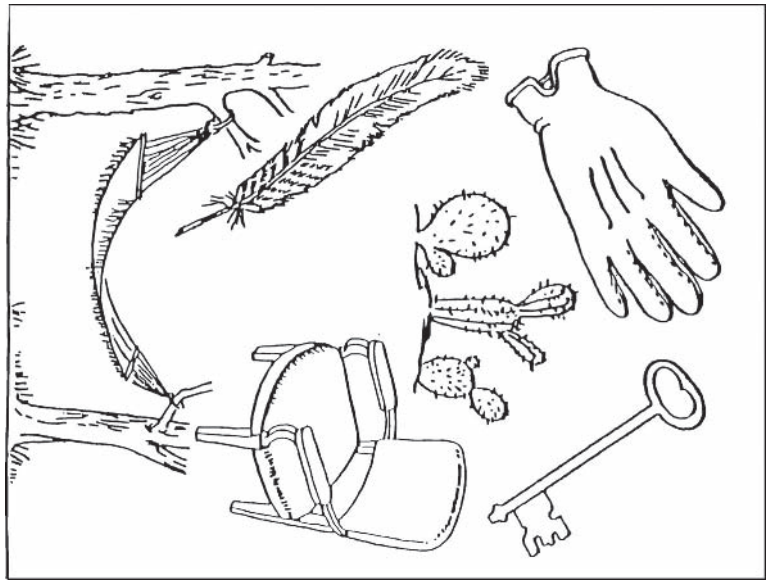

Figure A.1 (B) Naming testing for NIHSS (provided by NINDS).

(C)

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

Figure A.1 (C) Items for language and dysarthria testing for NIHSS (provided by NINDS).

(D)

MAMA

TIP-TOP

FIFTY-FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Figure A.1 (D) Items for language and dysarthria testing for NIHSS (Provided

Table A1.2 Modified Rankin Scale

Scale	Description of severity of disease
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Table A1.3 Barthel Index for chronic neurodisability*

Parameter	Finding	Points
Controlling bowels	Independent. Patient is able to control bowels and have no accidents	10
	Patient may occasionally have an accident or may require a suppository or enema	5
	Cannot meet defined criteria	0
Controlling bladder	Independent. Patient is able to control bladder day and night	10
	Patient may occasionally have an accident or cannot wait for a bedpan or is unable to get to the toilet in time	5
	Cannot meet defined criteria	0
Getting on and off toilet	Independent. Patient can get on and off toilet, adjust clothing, use toilet paper, and keep clothes from becoming soiled. The patient can use an object for support if needed	10
	With help	5
	Cannot meet defined criteria	0
Feeding	Independent. Patient can feed self if food is placed within reach. The patient may use an assistive device if needed. Eating needs to be accomplished within a reasonable time	10
	Some help is needed such as cutting up food	5
	Cannot meet defined criteria	0

Table A1.3 (*Contd.*)

Parameter	Finding	Points
Moving from wheelchair to bed and return	Independent in all phases of the activity	15
	With some minimal help or some supervision	10
	Requires assistance	5
	Cannot meet defined criteria	0
Walking on level surface	Independent. Patient can walk at least 50 yards without help or supervision (may use aid, such as a cane)	15
	With help	10
	Unable to walk but can propel a wheelchair independently	5
	Unable to walk and unable to propel a wheelchair	0
Dressing	Independent	10
	With help	5
	Cannot meet defined criteria	0
Ascend and descend stairs	Independent. Patient is able to go up and down a flight of stairs safely without supervision or help	10
	With help	5
	Cannot meet defined criteria	0
Grooming	Patient can wash, comb hair, and brush teeth. Men can shave themselves and women can apply makeup	5
	Cannot meet defined criteria	0
	Patient may use a bath tub, shower, or take a complete sponge bath unassisted	5
Bathing self	Cannot meet defined criteria	0

*Barthel Index = sum of points for all 10 items (minimum score 0, maximum 100).

Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index." *Maryland State Med Journal* 1965;14:56–61. Used with permission.

Table A1.4 Modified Hoehn and Yahr Scale

Stage of disease	Description of severity of disease
1	Unilateral involvement only
1.5	Unilateral and axial involvement
2	Bilateral involvement without impairment of balance
2.5	Mild bilateral involvement with recovery on pull test
3.0	Mild to moderate involvement; some postural instability but physically independent
4.0	Severe disability; able to walk and stand unassisted
5.0	Wheelchair-bound or bedridden unless aided

Table A1.5 Kurtzke Expanded Disability Status Scale (quantifies disability in multiple sclerosis)

1.0	No disability; minimal signs in one FS (functional system*)
1.5	No disability; minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid; self-sufficient; up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid; up and about much of the day; able to work a full day; may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately 5 meters even with aid; essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms; retains some self-care functions
9.0	Confined to bed; can still communicate and eat
9.5	Totally helpless bedbound patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

*Functional systems include pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other.

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